

ORGANIC SYNTHESIS

Volume 2

OPEN-CHAIN UNSATURATED COMPOUNDS

ALICYCLIC COMPOUNDS

AROMATIC COMPOUNDS

by

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PART I

OPEN-CHAIN COMPOUNDS

SECTION 2. UNSATURATED COMPOUNDS

CHAPTER 17

OLEFINIC COMPOUNDS

Methods of Preparation

By Dehydration of Alcohols

Unsaturated hydrocarbons may be prepared through the dehydration of alcohols either catalytically, or by use of dehydrating agents.

Catalytic dehydration may be carried out by passing the vapors of the alcohol through a tube heated to 350 to 550° and containing a contact agent¹ such as graphite, kieselguhr, kaolin, animal charcoal, pumice, etc. Metals or metallic oxides, especially aluminum oxide, quartz, red phosphorus, and the phosphate, sulfate or silicate of aluminum also may serve as catalysts.

A satisfactory alumina catalyst is obtained by adding an aqueous solution of ammonia to one of aluminum sulfate. The gelatinous precipitate formed is thoroughly washed by decantation; it is then mixed with granular pumice, the mixture is drained as completely as possible and dried at about 300°.

The effectiveness of catalysts is shown by the fact that ethyl alcohol, which remains unchanged when passed through a tube heated to 600°, is rapidly and completely dehydrated at 380° in the presence of aluminum oxide, and at 200-240° in the presence of red phosphorus.

High boiling tertiary alcohols such as methyldiphenylcarbinol,



are dehydrated when heated just below their boiling point. Dehydration may be accelerated by use of appropriate catalysts. Higher alcohols which boil with decomposition, such as cetyl alcohol, give olefins on strong heating. Cleavage of water takes place most readily from tertiary alcohols, and least readily from primary alcohols.

An aldehyde or a ketone also results during the catalytic dehydration of primary and secondary alcohols. Butyl alcohol and the higher alcohols generally yield mixtures of isomeric olefins.²

1,3-Butylene glycol, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{CH}_2\text{OH}$, is best dehydrated to *butadiene* by use of a primary sodium phosphate catalyst. The catalyst is prepared by impregnating granular graphite or coke with an aqueous solution of primary sodium phosphate containing a little free phosphoric acid. The impregnated mass is dried in a current of nitrogen and the temperature is then slowly raised to 250°. The finished catalyst should contain 12 to 20% of sodium pyrophosphate and about 2.5% free phosphoric acid.

Many substances may be employed as *dehydrating agents* in the preparation of olefins from alcohols. Sulfuric acid, potassium sulfate, zinc chloride, phos-

phorus pentoxide, phosphoric and metaphosphoric acids, boric anhydride and oxalic acid are most commonly used.³ Olefin formation takes place effectively at 180° in contact with anhydrous copper sulfate. Formic acid, acetyl chloride, phosphorus oxychloride, Grignard reagents, iodine and salts of weak bases with mineral acids have also been used.⁴ Elimination of water is apparently preceded by the formation of sulfuric ester of the alcohol when sulfuric acid is used as the dehydrating agent, the ester decomposing to the olefin on further heating. In many instances, the dehydrating action of the acid appears to be catalytic.⁵

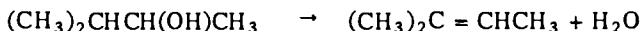
A satisfactory procedure for the preparation of ethylene and its immediate homologs consists in running the alcohol into syrupy phosphoric acid heated at 200-220;⁶ or the alcohol may be heated with potassium acid sulfate, or with aluminum sulfate. Dehydration may be effected also by adding the alcohol to zinc chloride heated to 200°. Olefins have been prepared successfully from a number of secondary and tertiary alcohols by heating with *p*-toluenesulfonic acid.⁷ Sulfuric acid may be used for the immediate homologs of ethyl alcohol, providing the amount of acid used is carefully regulated to prevent charring.⁸ In many cases sulfuric acid diluted with one or two volumes of water is used.

Tertiary alcohols and some of the higher secondary alcohols are successfully dehydrated on distilling with 4% of concentrated sulfuric acid.⁹ Tertiary alcohols and some secondary alcohols can be dehydrated by distilling with a small amount of iodine.¹⁰ Glycols have been dehydrated by heating with a small quantity of hydrobromic acid or trichloroacetic acid; pinacol has also been dehydrated by this procedure.¹¹

For the dehydration of terpenes, the use of oxalic acid is preferred in order to avoid molecular rearrangement. Menthols and menthadienes have been successfully dehydrated by means of aqueous solutions of oxalic acid.¹²

Dialkylvinylcarbinols can be dehydrated in the liquid phase by use of a small amount of aniline hydrochloride, bromide or toluene-*p*-sulfonate as a catalyst. The method is specific for olefinic alcohols.

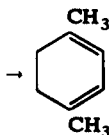
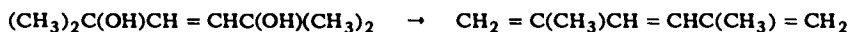
Where the possibility of the formation of isomers exists, these may form simultaneously during the process of dehydration,¹³ isobutyl alcohol, for example, giving *sym*-dimethylethylene and ethylethylene. The hydrogen atom eliminated in the process is abstracted to a large extent from the carbon atom bearing the least number of hydrogen atoms, while, when the olefin is hydrated, the hydrogen atom attaches itself to the carbon atom bearing the greater number of hydrogen atoms. This is known as Saytzev's rule.¹⁴ In accordance with this rule, the dehydration of isoamyl alcohol with sulfuric acid results largely in the formation of trimethylethylene:



While the hydration of trimethylethylene results in the formation of *tert*-amyl alcohol, $(\text{CH}_3)_2\text{C}(\text{OH})\text{CH}_2\text{CH}_3$.

In the process of dehydration, polymeric compounds may also be formed from alcohols with four or more carbon atoms. Changes in the structure of the carbon skeleton have also been observed, *unsym*-dimethylethylene resulting, for example, from isobutyl alcohol, $(\text{CH}_3)_2\text{CH}_2\text{CH}_2(\text{OH})$.

Dehydration of ethylenic glycols of the type $RR'C(OH)CH = CHC(OH)RR'$ generally results in the formation of dihydrofurans $RR'CCH = CHC(O)RR'$.³⁹² Dehydration takes place readily in acid solution even at room temperature.³⁹³ Loss of water occurs more readily from the freshly prepared glycol. Dehydration under drastic conditions may lead to the formation of dihydrobenzene derivatives:³⁹⁴

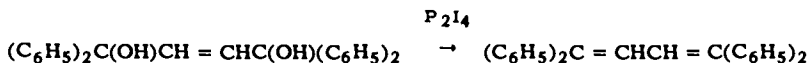


The dehydrating agents usually employed are 20% sulfuric acid, oxalic acid, 90% phosphoric acid; a mixture of sulfuric and acetic acids has also been used, as well as phosphorus tribromide in pyridine, acetic anhydride or iodine at 200°. ³⁹⁵

The glycol $C_6H_5CH_2CH(OH)CH = CHCH(OH)CH_2C_6H_5$ behaves exceptionally to give 1,6-diphenylhexatriene, $C_6H_5(CH = CH)_3C_6H_5$, on treatment with acetic anhydride, while the glycol $C_2H_5C(CH_3)(OH)CH = CHCH(OH)CH(CH_3)_2$ is converted to the triene alloocymene simply by heating. ³⁹⁶

The acetates of ethylenic glycols heated with copper bronze at 145-150° for 2 hours under reduced pressure yield trienes. ³⁹⁷

Dienes may be obtained from ethylenic glycols of the type under consideration by treatment with P_2I_4 in ether, chromous chloride in hydrochloric acid or vanadous chloride: ³⁹⁸



The method has been employed for the preparation of polyenes from polyethylenic glycols, and the synthesis of compounds related to carotenes. ³⁹⁹

α -Hydroxy acids are not converted, as a rule, to α,β -unsaturated acids on dehydration, but usually give lactides or aldehydes. In a few special cases α,β -unsaturated acids have been obtained, however, by a careful choice of the dehydrating agent. ¹⁵

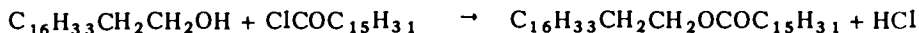
Acetals may be decomposed catalytically to vinyl ethers: ⁴⁰⁰



Yields of 90% have been attained by use of precious metal catalysts, conversions of 60 to 65% being obtained by a single pass.

Olefins by Pyrolysis of Esters

Higher alcohols and complex hydroxy compounds are best converted to unsaturated compounds via their esters with higher fatty acids by heating or distilling. Palmitic esters are suitable for the purpose; these may be obtained through the reaction of the hydroxy compound with palmitic acid chloride: ¹⁶

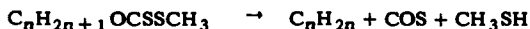


pyrolysis of the ester in this example gives octadecylene, $C_{16}H_{33}CH = CH_2$.

Many tertiary alcohols fail to yield an acetic ester when treated with acetyl chloride, but are converted to olefins. The transformation takes place with particular ease in the presence of a little zinc chloride.¹⁷

Pyrolysis of esters of higher fatty acids takes place under vigorous conditions and may result in the isomerization of the olefinic compound formed. *Tschugaëff's method*,¹⁸ which utilizes the methylxanthic esters of the alcohol, avoids isomerization, since the pyrolysis of these compounds takes place under comparatively mild conditions. Bornylene is obtained by this method in a fairly pure condition from borneol.

The sodium or potassium derivatives of the alcohol are converted to xanthates by the action of carbon disulfide; these are converted to their methyl esters and the latter are then distilled under atmospheric pressure



The method is especially suitable for the higher alcohols and has been most useful in the preparation of terpenes.

Olefins by Dehydrohalogenation or Dehalogenation of Organic Halides

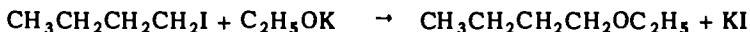
Olefins may be obtained through the removal of hydrogen halide from halo compounds by reaction with basic substances. Iodo compounds generally react quite readily, bromo compounds less readily, while chloro compounds are the least reactive. Normal halides are dehydrohalogenated less readily than secondary halides, and the latter less readily than tertiary halides.¹⁹ The rate of reaction is also influenced by the structure of the halide, more particularly by the number and position of the side chains, if such are present in the molecule of the compound. By-products are generally formed in considerable proportion on dehydrohalogenation of chloro compounds.

Trichlorohexane heated with alcoholic potassium hydroxide gives chlorodihydrobenzene, the remaining chlorine being rendered unreactive through the influence of the adjacent double bonds formed in the reaction.

Dehydrohalogenation may be effected by treatment of alkyl iodides with alkaline alcoholates:



Ether formation proceeds simultaneously in accordance with the equation:



This reaction proceeds to the greatest extent with normal alkyl iodides.

Hydrogen atoms in certain positions in some organic compounds are replaceable with bromine by the action of N-bromosuccinimide. Unsaturated bonds have been introduced into some bodies by bromination by this method followed by dehydrobromination.⁴¹⁵ Molecular rearrangements are not likely to take place in this method of introducing unsaturation, since both bromination and dehydrobromination may be carried out under mild conditions.

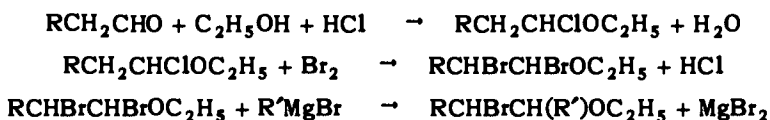
Alkylenes may be obtained by the removal of halogens from polyhalo com-

pounds by reaction with certain metals, such as zinc. Removal of halogen takes place most readily from those ethylenic compounds which add halogens with the greatest ease. This generalization is known as the *addition and fission rule of Michael*.²⁰ It may be stated in a more general form as follows:

The reaction between an unsaturated compound with an addend results in the formation of that one of two possible isomeric products which is the more easily converted to the original compound by cleavage of the addend.

Olefins by Boord's Method

In Boord's method, brominated ethers of the type $\text{RCH}(\text{OC}_2\text{H}_5)\text{CHBrR}'$ are heated with zinc dust to obtain olefins $\text{RCH}=\text{CHR}'$. This is an excellent method that has made possible the preparation of a large class of olefinic compounds, since the required bromo ethers are readily accessible from aldehydes by the following series of reactions:

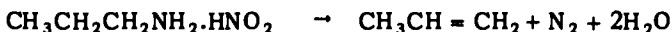


The bromoethers are obtained in good yield. The reaction with zinc dust proceeds slowly but yields are satisfactory.⁴⁰¹ A satisfactory method for the preparation of the dibromoethers consists in adding bromine to alkyl vinyl ethers, some of which are commercially available.

Miscellaneous Reactions Leading to the Formation of Olefins

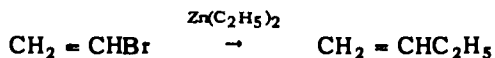
Alkylenes have been obtained from certain halohydrins by the removal of the elements of hypohalous acid, XOH ; thus, ethylene results on treatment of glycol bromohydrin, $\text{BrCH}_2\text{CH}_2\text{OH}$, with zinc dust and acetic acid.²¹

Alkylenes result in appreciable amounts through the decomposition of nitrous salts of primary amines by boiling their aqueous solution:²²

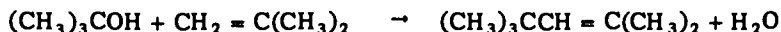


Olefins result also on heating alkylammonium phosphates,²³ and through the electrolysis of the potassium salt of certain saturated dicarboxylic acids, e.g. glutaric acid which yields propylene.²⁴

Homologs of olefins may be prepared through the reaction of brominated olefins with zinc alkyls:



Higher olefins may be prepared through the reaction of tertiary alcohols with an olefin hydrocarbon under the influence of zinc chloride or sulfuric acid:²⁵



Propylene results on passing a mixture of acetylene and methane over heated metals.²⁶

β -Isoamylene, $(\text{CH}_3)_2\text{C} = \text{CHCH}_3$, heated with methyl iodide, yields tetramethylethylene, $(\text{CH}_3)_2\text{C} = \text{C}(\text{CH}_3)_2$.

Wurtz type of condensation of two molecules of halo olefins has been effected by use of sodamide to obtain the trans polyenes 1,3,5,9-decapentene and 1,3,5,7,9,11,13-tetradecaheptene.

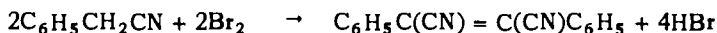
Olefins may be obtained by the partial reduction of acetylenic compounds. Partial reduction of dialkylacetylenes under mild conditions gives the *cis* isomer.⁴¹⁶ The *cis* isomers are obtained on reduction with Raney nickel. The *trans* isomers result, however, when the reduction is effected by sodium in liquid ammonia.⁴¹⁷

Addition compounds of olefins with zinc chloride, such as

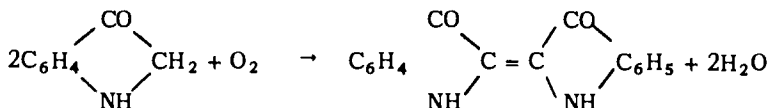


hydrated to the carbinol and converted to the corresponding chloride with hydrochloric acid, combine with olefins giving a saturated chloride, which on distillation yields an unsaturated compound.²⁷

Compounds having a *reactive methylene*, subjected to the action of oxidizing agents, may be condensed to an unsaturated product. Thus, diphenylmethane is converted to tetraphenylethylene when heated with sulfur to 240-250° or higher, and dicyanostilbene is obtained when benzyl cyanide is heated with bromine to 160-180°.²⁸

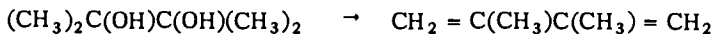


The formation of indigo through the oxidation of indoxyl by atmospheric oxygen,

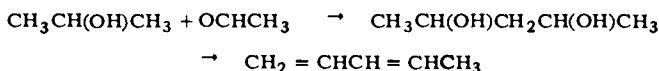


also represents an example of the method.

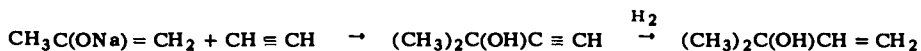
Unsaturated compounds with more than one double bond may be obtained by the methods employed for the preparation of compounds with a single bond. Thus, dienes are formed through the removal of the elements of water from glycols or olefinic alcohols by means of zinc chloride, potassium bisulfate or oxalic acid, or by distillation over heated aluminum hydroxide.²⁹



The glycol may be formed *in situ* through the reaction of an aldehyde and an alcohol over heated aluminum chloride:³⁰



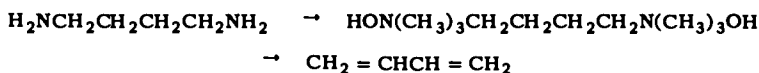
The olefinic alcohols may be prepared from α,β -unsaturated aldehydes or ketones and organo magnesium halides.³¹ They may be obtained also through the reaction of acetylene with acetone in the presence of sodium:³²



Treatment of allyl chloride and metallyl chloride with sodamide in liquid ammonia results in the formation of hexatriene and 2,5-dimethylhexatriene respectively.

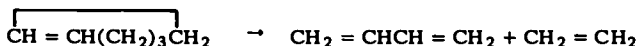
Elimination of hydrogen halides from dihalo compounds by use of alcoholic caustic, pyridine, quinoline, or by passing the vapors of the dihalide over heated soda-lime or other contact agents,³³ also takes place successfully in many instances, giving dienes.

Dienes may be obtained from diamines by conversion to quarternary ammonium compounds, by exhaustive methylation and by pyrolysis of the hydroxy compound:³²



Certain dienes are also prepared through the exhaustive methylation of cyclic nitrogen bases, piperylene, $\text{CH}_3\text{CH}=\text{CHCH}:\text{CH}_2$, resulting, for example as the final product of pyrolysis from the methylated product from piperidine.³⁴

Dienes result also through the pyrolysis of tetrahydrobenzene or its homologs:



Formation of Allenes

Dienes in which the two double bonds are contiguous, as in $\text{CH}_2=\text{C}=\text{CH}_2$, are known as allenes. Only a few representatives of this class of compounds are known.

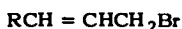
Two methods of fairly general applicability are available for the preparation of such compounds; removal of bromine from unsaturated dibromo compounds of the type $\text{RR}'\text{CHBrCBr}=\text{CH}_2$ with zinc,³⁶ and dehydration of unsaturated alcohols of the type $\text{RR}'\text{C}=\text{C(OH)R}''\text{R}'''$.³⁵

Allene itself, $\text{CH}_2=\text{C}=\text{CH}_2$, may be obtained by dehydrohalogenating 1,2,3-tribromopropane with solid potassium hydroxide and heating the resulting product with zinc.³⁶ It may also be obtained by the electrolysis of potassium itaconate.

Methylallene is obtained through the dehalogenation of tetrachlorobutane:³⁷

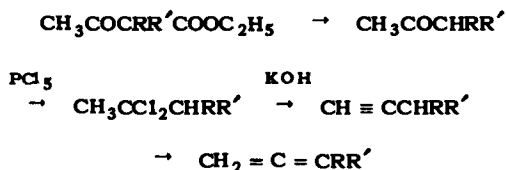


Allenes $\text{RCH}=\text{C}=\text{CH}_2$ have been prepared from alcohols $\text{RCH(OH)CH}=\text{CH}_2$ by first treating the latter with phosphorus tribromide to obtain the monobromides



brominating these at 0° to the tribromides $\text{RCHBrCHBrCH}_2\text{Br}$, fusing the tribromides with 75 to 80% potassium hydroxide to obtain the allene dibromides $\text{RCHBrCBr}=\text{CH}_2$. Allenes result on adding these dropwise to zinc dust suspended in boiling alcohol.⁴¹⁸

Unsym-dimethylallene may be prepared from trimethylethyl dibromide by dehydrobromination. Dialkylated allenes may be prepared from dialkylacetoacetic esters, by decarboxylation followed by successive treatment with phosphorus pentachloride and alcoholic potassium hydroxide:



The addition of one mole of bromine to allenes $\text{RCH} = \text{C} = \text{CH}_2$ occurs mainly at β, γ -positions, while the addition of a second molecule results in the formation of the $\alpha, \beta, \beta, \gamma$ -tetrabromo derivative. Treatment of allenes of this type with concentrated sulfuric acid at -10° , followed by the addition of water, results in the formation of the ketones $\text{RCH}_2\text{COCH}_3$. Sodamide reacts with such allenes to form the sodium derivative of the isomeric acetylenes, $\text{RCH}_2\text{C} \equiv \text{CNa}$.

Polyenes; Carotenoids⁴¹⁹

Polyenes, i.e., compounds containing several olefinic bonds, occur extensively in nature; they include the important class of compounds known as carotenoids. They are of importance in vitamin chemistry, and their synthesis has assumed considerable importance.

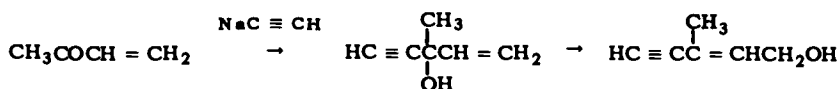
Only a few naturally occurring carotenoids have been synthesized to date, though considerable progress has been made in the synthesis of related bodies. The Grignard reaction involving acetylenic bodies and unsaturated carbonyl compounds of varying chain length derived from ionone has been made use of in building up the desired chain length in such syntheses. The comparable reaction of alkali metal acetylides with carbonyl compounds, and the Reformatsky reaction have also been utilized. In a few instances a modified Wurtz type reaction has been resorted to to establish the carbon to carbon linkage. The carbinols resulting from the Grignard condensation and similar reactions are dehydrated to produce additional olefinic linkages at desired locations. Dehydration is usually effected by heating with *p*-toluenesulfonic acid in toluene solution, refluxing for 15 minutes often bringing about the desired result. Dehydration is usually accompanied with a realignment of the olefinic linkages. It has been observed that the acid catalyzed dehydration-rearrangement of β -ionols gives only a small yield of β -ionylidene compound, the principal product being the isomeric retroionylidene compound which contains the ring structure⁴²⁰



The acetylenic bonds in the products resulting from condensation reactions involving acetylenic compounds are selectively reduced to olefinic bonds at some appropriate stage in a synthesis involving numerous steps. Reduction is effected catalytically using, for example, a palladium-charcoal catalyst poisoned with quinoline.

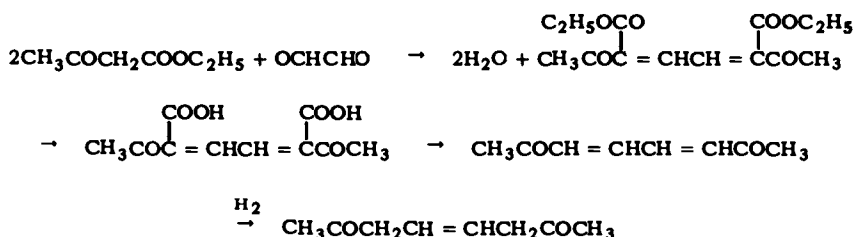
A number of intermediates of special structure have been prepared that have been employed in the synthesis of carotenoids.

A 6-carbon acetylenic alcohol has been prepared by condensing methyl vinyl ketone with sodium acetylide in liquid ammonia and subjecting the product to an allylic rearrangement by treatment with 10% sulfuric acid:⁴²¹

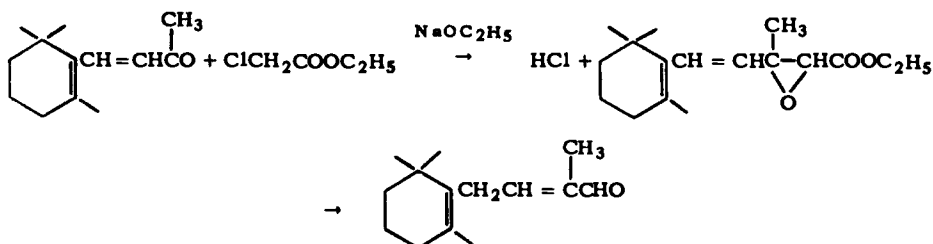


The corresponding bromo compound has been made from this by replacing the hydroxyl group with bromine by treatment with phosphorus tribromide.⁴²² A 12-carbon diacetylenic hydrocarbon, $\text{HC}\equiv\text{CC}(\text{CH}_3)=\text{CHCH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{C}\equiv\text{CH}$, has been made from the bromide by heating with zinc dust in the presence of some iodine. Tautomeric bodies are formed in large proportion in this reaction; much better results are obtained when the coupling is brought about by means of the zinc-copper couple.

An olefinic 8-carbon dione, octenedione, has been synthesized, although in very low yield, by condensing glyoxal with acetoacetic ester in the presence of pyridine, then hydrolyzing and decarboxylating the resulting compound and finally partially reducing the diene obtained:



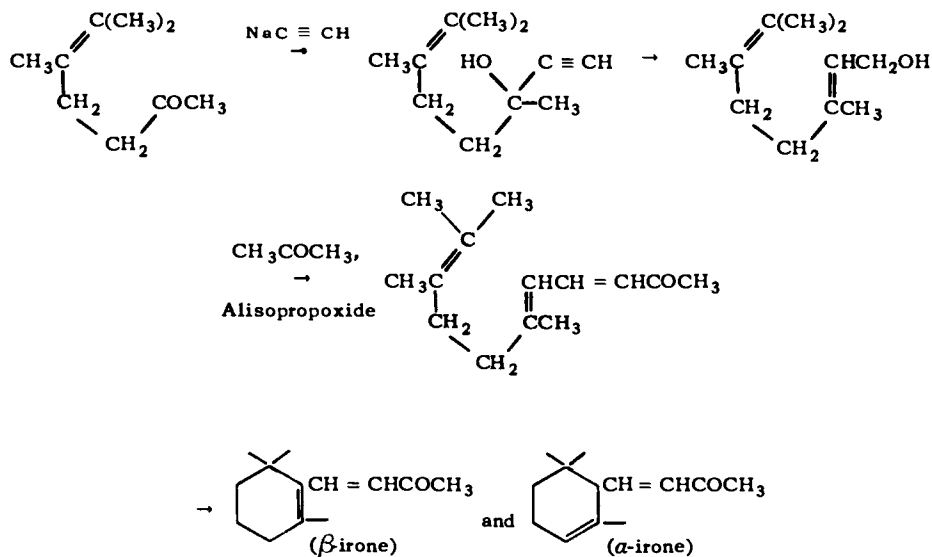
A 14-carbon aldehyde has been prepared from β -ionone and ethyl chloroacetate by Darzen's condensation at -30° , then saponifying the compound formed at -5° , and decarboxylating the resulting acid:⁴²⁴



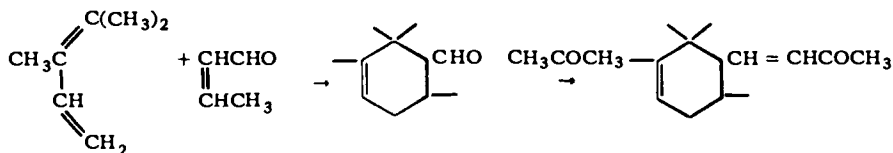
The reaction is best carried out in the absence of a solvent, and the ester is hydrolyzed with cold 20% alcoholic caustic.

A 14-carbon epoxide has been prepared from 2,2,6-trimethylcyclohexanone by condensation with acetylene, reaction of the halomagnesium derivative of the resulting compound with monochloroacetone and dehydrochlorination with caustic.⁵³⁸

Irone, a 14-carbon ketone, has been synthesized from 2,3-dimethylheptene-2-one-6, by condensation with sodium acetylide, partial hydrogenation followed by an allylic rearrangement, and finally Oppenauer oxidation in the presence of acetone to *psuedo* irons, which was subsequently cyclized to a mixture of α - and β -irones with phosphoric acid:⁵⁴¹

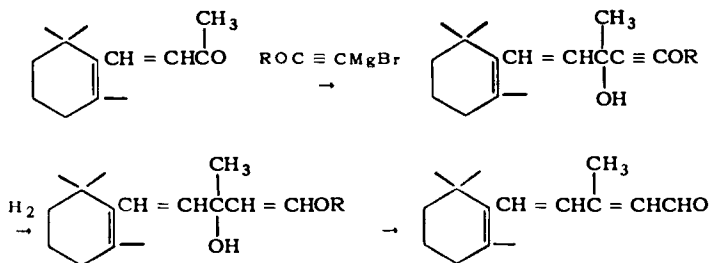


Isoirone, another 14 carbon ketone, has been obtained from trimethylbutadiene and crotonaldehyde by diene synthesis, followed by condensation with acetone:⁵⁴²



The isomeric 2,3,3,4-tetramethylcyclohexene-4-al-1 is formed simultaneously with the desired aldehyde in the diene synthesis, but the two aldehydes are readily separated after conversion to the respective phenylhydrazones.

Ionylideneacetaldehyde, which has a 15 carbon skeleton, has been prepared from β -ionone by condensation with ethoxyacetylenemagnesium bromide, partial reduction of the product and an allylic rearrangement and hydrolysis with hydrogen chloride:⁵⁴³

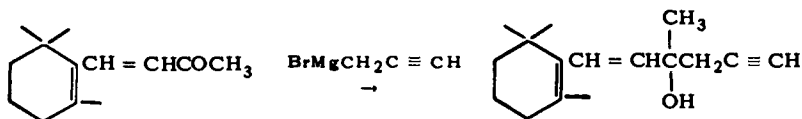


Another synthesis of the compound has been achieved from ionylideneacetic acid, which was converted to its *o*-toluidide, treated with phosphorus pentachloride and the resulting

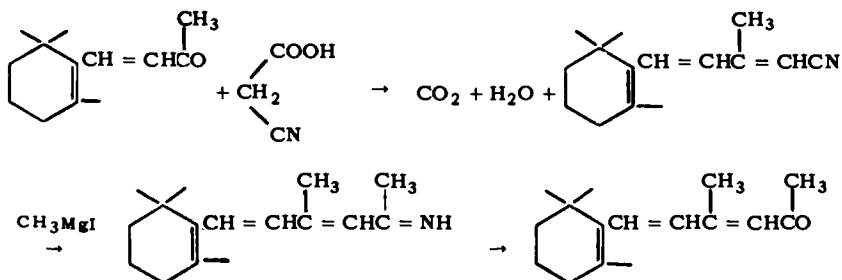
chloro compound was reduced to the toluimide of the aldehyde, hydrolysis of which gave the aldehyde.⁵⁴⁴ This method apparently yields an impure product.⁵⁴⁵

β -Ionylideneethane has been made through the interaction of β -ionone with ethyllithium and dehydration of the resulting alcohol.⁵⁴⁶

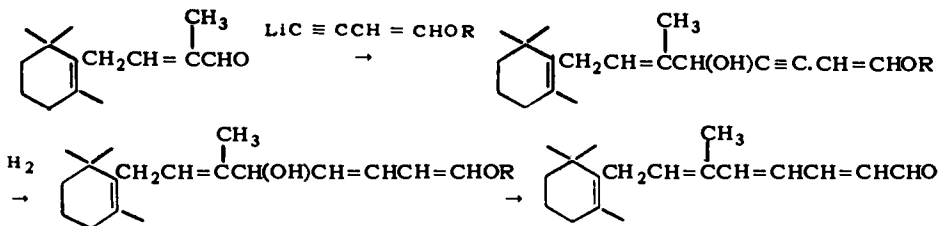
A 16-carbon ethynyl carbinol has been made from ionone and propargyl bromide:⁴²⁵



A 16-carbon ketone, ionylideneacetone, has been prepared through the condensation of β -ionone with cyanacetic acid, reacting the resulting cyano compound with methylmagnesium iodide, and hydrolyzing the ketimine formed:⁵⁴⁷

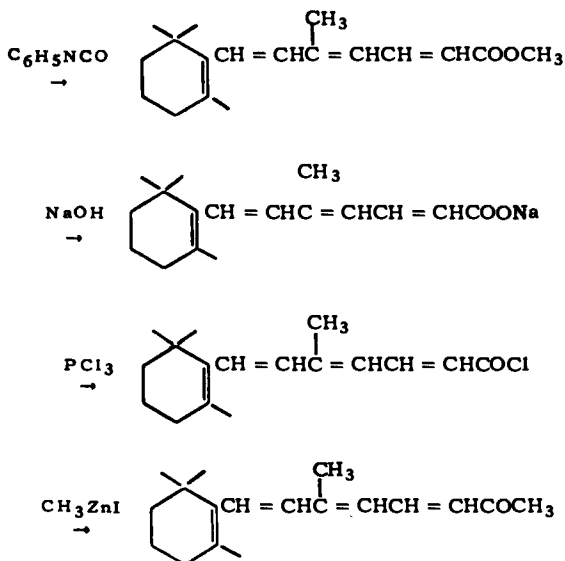


An 18-carbon aldehyde has been prepared from the 14-carbon aldehyde by condensation with the lithium compound of ethoxyvinylacetylene, partial reduction of the resulting acetylenic enol ether catalytically in the presence of poisoned palladium catalyst to the corresponding ethylenic enol ether, and finally hydrolysis of the latter at room temperature with 1% alcoholic sulfuric acid.⁴²⁶



An 18-carbon ketone has been prepared from α -ionone by condensing the compound with γ -bromocrotonic acid in the presence of zinc, dehydrating the resulting ester by heating with phenyl isocyanate, converting the triply unsaturated C_{17} ester to the corresponding acyl chloride by alkaline hydrolysis followed by treatment with phosphorous trichloride, and finally treating the acyl chloride with methylzinc iodide:⁴²⁷

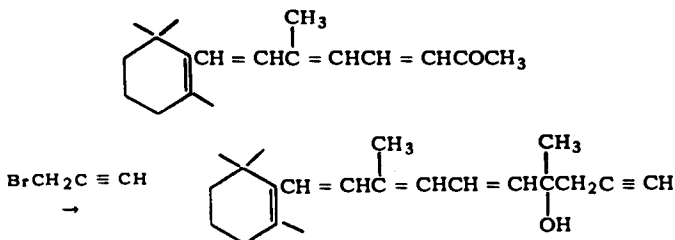




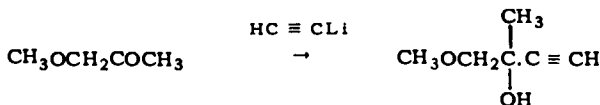
γ -Bromocrotonic ester may be prepared from crotonic ester by the action of N-bromo-succinimide.⁵³⁹

The C_{18} ketone has also been prepared from isonylidene acetic acid which was reduced with lithium aluminum hydride to the corresponding alcohol and this was condensed with acetone in the presence of aluminum *tert*-butoxide.⁵⁴⁰

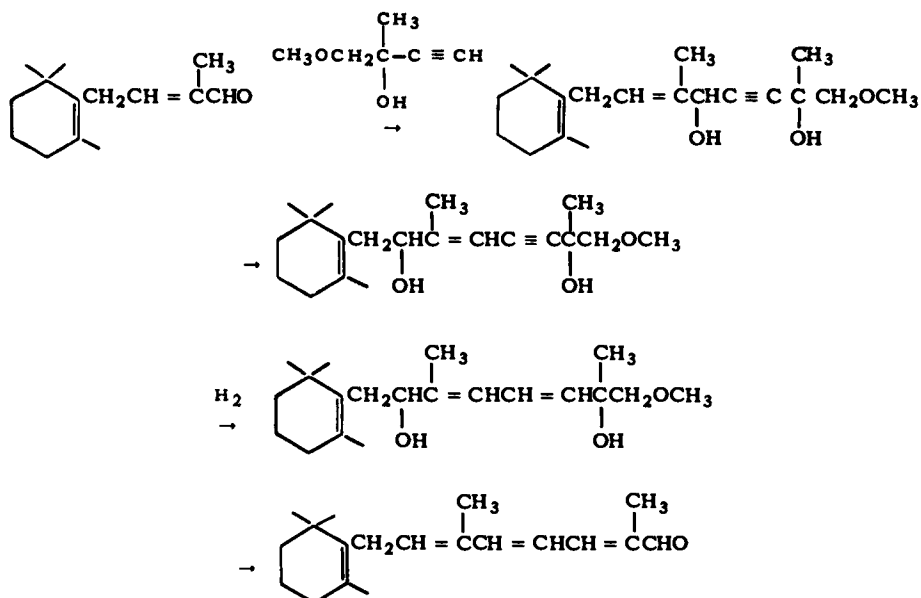
A 21-carbon ethynyl carbinol has been prepared from the C_{18} ketone by reaction with propargyl bromide in the presence of zinc:⁴²⁸



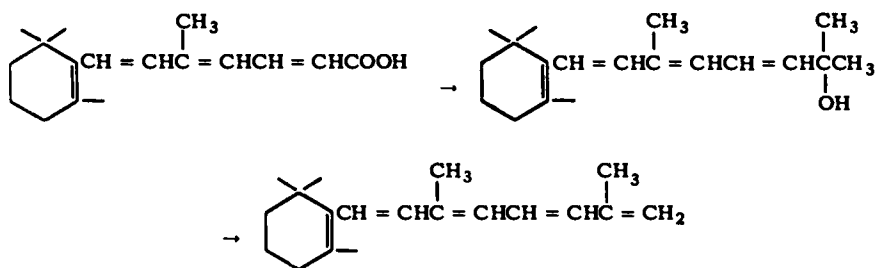
A 19-carbon aldehyde has been synthesized from the C_{14} aldehyde and an acetylenic diol half ether obtained by condensing lithium acetylide with acetol ether:



Condensation of the diol ether with the C_{14} aldehyde results in the formation of an acetylenic triol monomethyl ether, which, after being subjected to an allylic rearrangement, is selectively reduced to the corresponding ethylenic compound, and the latter is partially dehydrated. A half acetal is formed thereby, which changes spontaneously to the C_{19} aldehyde:⁴²⁹

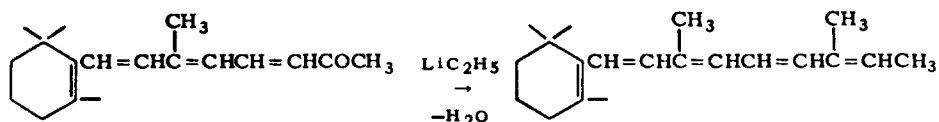


A 19-carbon hydrocarbon has been prepared from ionylidenecrotonic acid by reaction with lithium methyl to obtain a C₁₉ carbinol, which was dehydrated to the hydrocarbon: ⁵⁴⁸



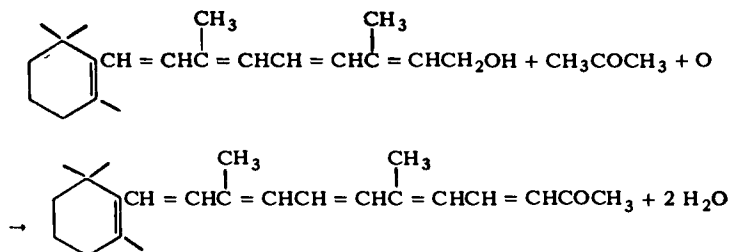
The compound has been obtained also by condensing α-ionone with formic ester to hydroxymethylene ionone, the tautomeric aldehyde form of which reacting with methallylmagnesium bromide yields a diol; dehydration of the latter gives the hydrocarbon. ⁵⁴⁹

A 20-carbon hydrocarbon, *axerophthen*, which is related to vitamin A₁, has been prepared from the C₁₅ ketone by reaction with lithium ethyl and dehydration of the resulting carbinol: ⁵⁵⁰



The compound has been prepared by an alternative method involving the condensation of the C₁₅ aldehyde with methyl ethyl ketone, reaction of the resulting keto compound with lithium methyl, and finally dehydration of the product. ⁵⁵¹

A 23-carbon ketone has been prepared through the condensation of acetone with vitamin A alcohol in the presence of aluminum *tert*-butylate:⁴³⁰

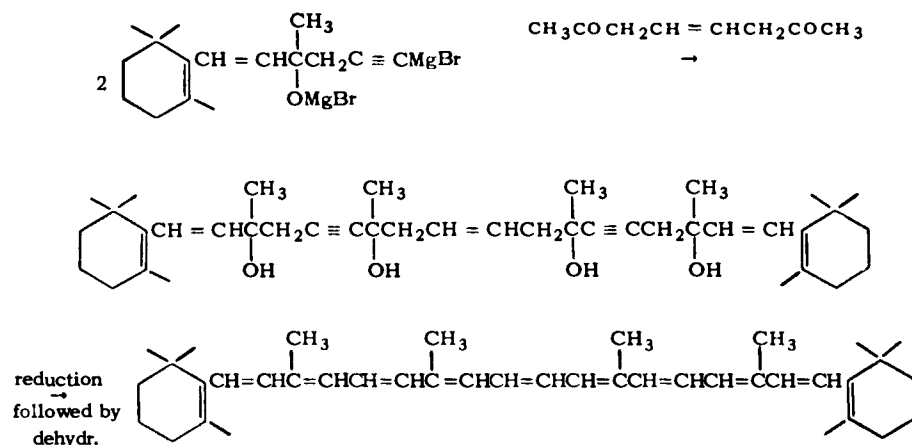


A 26-carbon ethynyl carbinol has been prepared from the C_{23} ketone by condensation with propargyl bromide in the presence of zinc.

Synthesis of Some Representative Carotenes

A brief description of the synthesis of a number of representative carotenoids is presented below.

β -Carotene⁴³¹ has been synthesized through the condensation of the C_{16} ethynyl carbinol with octenedione, forming a C_{40} diyne tetrol. This has been reduced with partially deactivated palladium catalyst, and the product dehydrated by boiling with a toluene solution of *p*-toluenesulfonic acid:



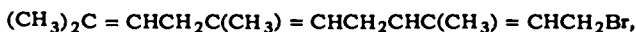
A *cis* isomer is formed when the reduction of the acetylenic bond is carried out in the dark at a low temperature. The *cis* isomer may be transformed to the *all trans* isomer by subjecting the compound to the action of light for 3 hours, or by heating it at 70° for $1\frac{1}{2}$ hours, though isomerization by light is the preferable method, since it produces a minimum amount of byproducts. Isomerization may be brought about within 3 minutes with iodine, but a mixture of isomers is obtained by this method. β -Carotene has been isolated in the pure form by careful chromatographic fractionation. Separation may be effected efficiently by use of active alumina or magnesium oxide in a Tswett column. The extent of adsorption is dependent on the number of conjugated double bonds and the number of hydroxyl groups in the carotenoid. Xanthophylls are adsorbed in preference to the hydrocarbon pigments, and in proportion to the number of hydroxyl groups

present. The condensation of the ethynyl carbinol with octenedione has also been effected via the lithium derivative of the acetylenic compound with improved yields.⁴³² *ε*-Carotene has been prepared by the same method from the α -isomer of the 16-ethynyl carbinol.⁴³³ β -Carotene has been synthesized also from the C₁₉ aldehyde and acetylenedimagnesium bromide;⁴³⁴ also from the C₁₄ aldehyde and 1-methoxy-2-methylbut-3-yne.

Isocarotene or dehydro- β -carotene is obtained by treatment of the tetraiodide of β -carotene with acetone.⁵⁵² It has been claimed that racemic α -carotene has been synthesized from a mixture of α - and β -ionone acetylenic carbinols and octenedione,⁵⁵³ and that γ -carotene has been obtained similarly from a mixture of acetylenic carbinols made from α - and γ -ionones.⁵⁵⁴ A carotenoid with two α -ionone rings has also been synthesized.⁵⁵⁵

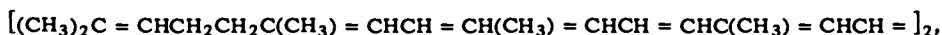
Higher homologs of carotene have been prepared from longer chain intermediates. A carotene homolog with 42 carbon atoms has been synthesized from β -C₁₉ aldehyde and diacetylene.⁴³⁵ *Decapteno- β -carotene* has been prepared from the halomagnesium compound of 21 carbon ethynyl carbinol and octenedione to form a C₅₀ diacetylenic tetrol; the carotene analog has been obtained from this by selective hydrogenation and dehydration. *Dodecapreno- β -carotene* has been made from octenedione and the C₂₆ ethynyl carbinol prepared from vitamin A alcohol as previously described.⁴³⁰

Squalene has been obtained from farnesyl bromide,



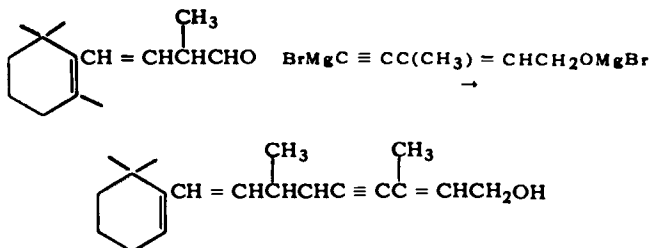
by the Wurtz reaction using potassium or magnesium to effect coupling.⁴³⁶

Lycopine,

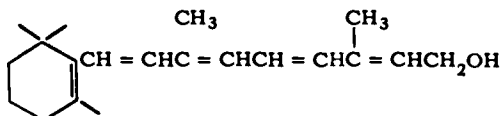


has been prepared from pseudoionone by the following steps: condensation with propargyl bromide in the presence of zinc and a little iodine; reaction of the halomagnesium compound of the resulting acetylenic compound with octanedione; partial reduction of the diacetylenic compound formed to the corresponding olefinic body; and finally, dehydration with *p*-toluenesulfonic acid.⁴²³ The compound was isolated chromatographically with calcium hydroxide.

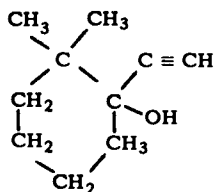
Condensation of the C₁₄ aldehyde and the halomagnesium derivative of the C₆ acetylenic alcohol gives an acetylenic alcohol containing the carbon skeleton of vitamin A₁:⁴³⁷



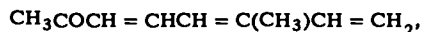
Partial reduction of the acetylenic bond in this compound to an ethylenic bond, followed by selective acetylation, dehydration with a petroleum ether solution of iodine, and finally saponification yields vitamin A₁,



Another synthesis of Vitamin A₁ makes use of the condensation product of 2,6,6-trimethylcyclohexanone and acetylene



The steps involved are condensation of this compound with the ketone,

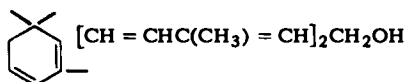


an anionotropic rearrangement, acetylation of the primary hydroxyl group, partial hydrogenation, and finally dehydration to vitamin A₁ acetate.⁴³⁸

Another synthesis of vitamin A starts with ionylideneacetaldehyde which was condensed with β -methylcrotonaldehyde in the presence of pyridine to vitamin A aldehyde.⁵⁵⁶ The overall yield of vitamin A by this method was 7.5%.

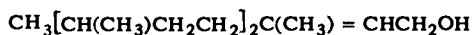
The synthesis of vitamin A acid has been achieved also from C₁₈ ketone, by subjecting this to the Reformatsky reaction with ethyl bromoacetate and dehydration and saponification of the resulting ester.⁴²⁷ The ester of vitamin A acid may be converted to vitamin A alcohol by reduction with lithium aluminum hydride.⁵⁵⁷ Vitamin A alcohol has been made by condensing the C₁₈ ketone with ethoxyacetylene to an acetylenic carbinol, partially hydrogenating this, and subjecting the product to an anionotropic rearrangement under the influence of hydrogen chloride. The resulting aldehyde was subsequently reduced to vitamin A alcohol.⁵⁵⁸

Treatment of the methyl ester of vitamin A acid with N-bromosuccinimide yields a 3-bromo derivative from which the methyl ester of vitamin A₂ has been obtained by dehydrobromination with N-phenylmorpholine; reduction of the purified ester with lithium aluminum hydride leads to the formation of vitamin A₂

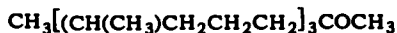


An analog of vitamin A acid with a triple bond and a cyclohexene ring has been prepared from the Grignard compound of ethynylcyclohexene and crotonylideneacetone by condensation followed by an anionotropic rearrangement, Oppenauer oxidation of the resulting fully conjugated alcohol, and the condensation of the ketone obtained with ethyl bromoacetate by the Reformatsky reaction.⁵⁵⁹ The corresponding analog of Vitamin A alcohol has been synthesized by condensation of ethynylcyclohexene with vinylcrotonylideneacetone, and rearrangement of the resulting carbinol with dilute acid.⁵⁶⁰

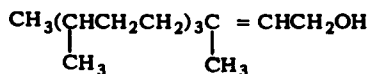
Phytol has been synthesized from pseudoionone by the following steps: Reduction to a saturated ketone, condensation of this with acetylene in the presence of sodium amide, partial reduction of the resulting acetylenic alcohol to the corresponding olefinic alcohol, rearrangement followed by acetylation and hydrolysis to the alcohol,



Replacement of the hydroxyl group with bromine by use of phosphorus tribromide, condensation of the bromide with acetoacetic ester in the presence of sodium ethoxide, followed by hydrolysis and reduction of the ethylenic bond gave the ketone



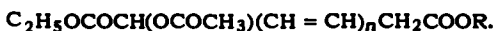
Further condensation of this with acetylene, reduction to the tertiary olefinic alcohol, and finally rearrangement to a primary alcohol gave phytol,⁴³⁹



A method has been evolved for the preparation of a dicarboxylic ester,

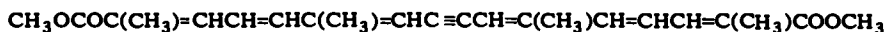
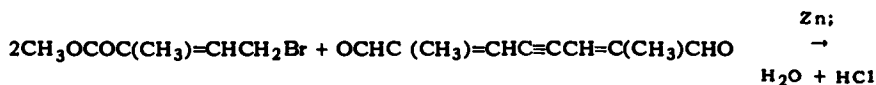


from the monocarboxylic ester, $\text{CH}_3(\text{CH} = \text{CH})_n \text{COOR}$, which consists in condensing diethyl oxalate with the latter in the presence of potassium ethoxide, or preferably, rubidium ethoxide, to obtain $\text{C}_2\text{H}_5\text{OCOCOCCH}_2(\text{CH} = \text{CH})_n \text{COOR}$.⁴⁴⁰ Treatment of this with acetic anhydride gives $\text{C}_2\text{H}_5\text{OCOC}(\text{OCOCH}_3) = \text{CH}(\text{CH} = \text{CH})_n \text{COOR}$, which on reduction with aluminum amalgam is converted to

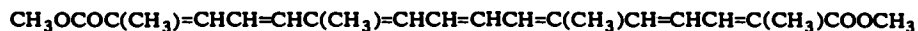


On treatment of this with methanolic potassium hydroxide the elements of acetic acid are removed with the formation of $\text{C}_2\text{H}_5\text{OCO}(\text{CH} = \text{CH})_{n+1} \text{COOR}$. A series of these compounds up to $n = 6$ have been prepared by this method. Aluminum amalgam reduction tends to replace the acetoxy group by a hydrogen in the higher members of the series, though the resulting dicarboxylic acid can be dehydrogenated by atmospheric oxygen in the presence of alkali.⁴⁴¹

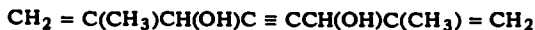
Crocetin dimethyl ester has been synthesized from the methyl ester of α -methyl- γ -bromoangelic acid and a C_{10} acetylenic dialdehyde by Reformatsky's reaction and partial catalytic reduction:⁵⁶¹



H_2, Pd



The dialdehyde required in the synthesis was prepared from the glycol obtained by the condensation of α -methylacraldehyde with acetylene, by oxidation of the product resulting from a molecular rearrangement with manganese dioxide:⁵⁶²

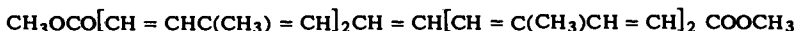


MnO_2

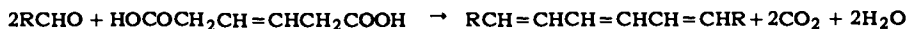


Trans methyl bixin has been synthesized⁵⁶³ from the tetrahydropyranyl ether of 2-methylpent-2-en-4-yn-1-ol by reacting two moles of the lithium derivative of this compound with one of the 8-carbon diketone to obtain, after dehydration, a crystalline diether. Hydrolysis of the latter to the corresponding diol, oxidation with manganese dioxide to the corresponding dialdehyde and a double Doebner condensation with ma-

ionic acid gave, after esterification with diazomethane, a diacetylenic ester. Partial catalytic reduction of this compound gave *trans*-methyl bixin,



Polyene hydrocarbons have been prepared from unsaturated aldehydes.⁵⁶⁴ In one method the aldehyde was condensed with succinic or dihydromuconic acid in the presence of lead oxide:



Polyenes with up to eight conjugated double bonds have been prepared in this manner, but the method fails when one attempts to prepare polyenes with a greater number of conjugated double bonds.

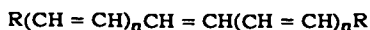
The hydrocarbon $\text{CH}_3(\text{CH} = \text{CH})_3\text{CH}_3$ has been prepared from the glycol,



which has been obtained in turn from crotonaldehyde. Syntheses of higher hydrocarbons of the type $\text{CH}_3(\text{CH} = \text{CH})_n\text{CH}_3$ have been accomplished through the reaction of ethylmagnesium bromide with aldehydes $\text{CH}_3(\text{CH} = \text{CH})_{n-1}\text{CHO}$, and dehydration of the alcohols obtained with 1% *p*-toluenesulfonic acid in ether. The first colored polyene hydrocarbon to be synthesized, $\text{CH}_3(\text{CH} = \text{CH})_6\text{CH}_3$, has been prepared by this method.

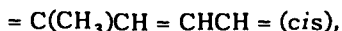
Aldehydes $\text{CH}_3(\text{CH} = \text{CH})_n\text{CHO}$ with *n* up to 5 have been prepared by the self-condensation of acetaldehyde in the presence of pyridine,⁵⁷⁰ and through the self-condensation of crotonaldehyde in the presence of piperidine acetate.⁵⁷¹ Polyene acids with an additional ethylenic group have been obtained through the condensation of polyene aldehydes with malonic acid in the presence of pyridine. Aldehydes with more than seven ethylenic bonds undergo this condensation in preference to self-condensation, but the reverse holds true of aldehydes with fewer than seven ethylenic bonds. With the latter, reaction proceeds satisfactorily only in the presence of piperidine. The higher aldehydes yield dicarboxylic acids, while the lower members give monocarboxylic acids. Partial decarboxylation of dicarboxylic acids may be effected by boiling with a mixture of acetic acid and acetic anhydride.

Thioaldehydes $\text{R}(\text{CH} = \text{CH})_n\text{CHS}$ may be desulfurized to



by means of certain reducing bodies. 1,22-Diphenyldocosaundecaene, a violet-black substance with a metallic lustre, and 1,30-diphenyltriacontapentadecaene, the highest known member of the polyene hydrocarbon series, have been prepared by this method.

In connection with polyenes, a postulate put forward by Pauling should be pointed out. This states that the highly hindered system



is sufficiently unstable to be non-existent.⁴⁴² There is some doubt, however, about the absolute validity of this hypothesis.

Properties of Olefin Hydrocarbons

The lower olefins are gases, olefins of medium molecular weight are liquids, while olefins with sixteen or more carbon atoms in their molecule are solids. Unsaturated hydrocarbons have boiling points a few degrees above those of the

corresponding saturated compounds. Substituted ethylenes are capable of forming molecular complexes with many compounds.

The presence of an unsaturated bond in a compound may influence the relative stability of neighboring bonds. The effect of the double bond on the reactivity of halogens attached to an unsaturated carbon atom or to an adjacent atom has already been pointed out. Certain other cases of activation may here be pointed out. The unsaturated system $-C = C-$, when attached to a methylene group, causes an increase in the reactivity of the methylenic hydrogen atoms. The enhanced reactivity of the methylene group in styrene may be ascribed to the combined effect of the unsaturated bonds and the phenyl group.⁴⁰

The influence of a group A attached to the vinyl group $-C(E_1) = CE_2-$ on the reactivity of centers in E_2 may, apparently, be transmitted through a number of vinyl groups $-CH = CH-$ interposed between A and E_2 (*Principle of Vinyl-ogy*)⁴¹. As a general rule, conjugated systems are characterized by this ability to transmit a type of reactivity, alternate atoms acquiring similar properties or reactivities.

The phenomenon of *chelation* observed with some unsaturated hydroxy carbonyl and hydroxy nitro compounds is another manifestation of the effect of the unsaturated bond.

It has been observed that the double bond between two carbon atoms strengthens the following single carbon bond, and weakens the next following. This alternation of strong and weak single carbon bonds goes through the entire carbon chain with decreasing energy. This generalization is known as the *double bond rule*.

The grouping $C = CHOH$ is not stable and immediately undergoes rearrangement to a saturated carbonyl group $CHCHO$, a generalization which is known as *Erlenmeyer's rule*.⁴² The grouping $C = CHOR$ is, however, stable and ethers of this type, such as $CH_2 = CHOC_2H_5$ and $CH_2 = C(OC_2H_5)CH_3$, are known. Compounds having the structure $RCOCH = CHOH$ form an exception to this rule and are quite stable.

Dienes containing conjugated double bonds behave in a characteristic manner in many of their reactions. They often undergo the so-called 1,4-addition. Additions of this type occur on reduction with nascent hydrogen and on halogenation, although halogens simultaneously add also at the 1,2-positions.⁴³ The presence of a carbethoxy, a phenyl or an unsaturated grouping in 1 or 4 position or in both positions induces addition at 1,2- or 3,4-positions.⁴⁴ Halogen acids and nitrogen tetroxide give 1,2-addition products. Catalytic hydrogenation eliminates all unsaturation and partial hydrogenation by this method has not been observed. The Diels-Alder diene synthesis, which is dealt with in Chapter 20, represents a typical example of 1,4-addition.

Alkyl groups attached to an unsaturated carbon atom influence the reactivity or mobility of the bond between the other unsaturated carbon atom and the group attached to it. This effect may be ascribed to the hydrogen atoms attached to the α -carbon atom in the alkyl group and is distinct from the inductive effect of the alkyl group. It may be considered the result of a type of tautomerism and

is termed the *Baker-Nathan effect* (hyperconjugation).⁴⁵ It is greatest with the methyl group, less with the ethyl group and still smaller with the isopropyl and *tert*-butyl groups.

In compounds containing the structural unit $\text{C.C.C}'\text{.C.C}'\text{.C.C}$ it is impossible to establish ethylenic linkages between the carbon atoms C' and an adjacent carbon atom. Reactions that may be expected to lead to the appearance of such linkages generally result in the rupture of the $\text{C}'\text{--C}$ linkage; or if such rupture fails to occur, the unsaturated bond migrates to another position. It follows that cyclization of the structure $\text{C}''\text{.C}' = \text{C}'\text{.C}(\text{C}'')\text{.C}$ by union between the carbon atoms designated C'' can not be carried out without migration of the double bond between the carbon atoms designated C' . This is known as *Bredt's rule*.⁴⁶

Nascent hydrogen does not generally attack olefinic double bonds, tetraphenylethylene forming an exception. No method has yet been discovered for reducing the double bond in compounds with the diphenylated cyclic nucleus⁴⁴³



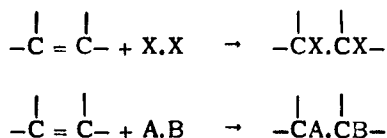
Determination of Unsaturation

A qualitative test for the presence of a double bond in a compound is the yellow color developed with tetranitromethane. α,β -Unsaturated ketones fail to give the reaction.⁵²³

Various methods have been employed for the estimation of degree of unsaturation. A determination of iodine number or bromine or thiocyanogen number are often sufficiently reliable. The action of ozone is unreliable, and oxygen take up from perbenzoic acid does not always give satisfactory results.⁵²⁴ Catalytic hydrogenation often gives an accurate measure of the degree of unsaturation, but this method fails with compounds in which the olefinic linkage is in α,β -position to a carbonyl group.⁴⁵⁹

Addition Reactions of Olefins

The presence of the reactive double bond in olefinic compounds makes possible the addition of elements or groups to these compounds at the point of unsaturation, in accordance with the scheme



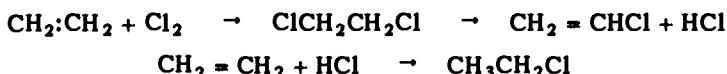
Thus, halogens add to many olefinic hydrocarbons to form saturated dihalo

compounds; hydrogen halides yield saturated monohalo derivatives. Addition compounds may be obtained also with sulfur dioxide, hydrogen sulfide, nitrogen oxides, and many other compounds.

The reactivity of the ethylenic bond in unsaturated compounds is influenced by groups in the vicinity of the double bond. Methyl groups, which have the property of repelling electrons, facilitate the addition of reagents such as bromine. The carboxyl group deactivates the double bond. The phenyl group also causes deactivation. Bromine in vinyl bromide causes deactivation, but this halogen may be expected to cause activation under certain circumstances.

Addition of Halogens

The addition of chlorine to olefin hydrocarbons generally takes place with great vigor and with evolution of heat when the pure compounds are brought together with undiluted chlorine. The reaction proceeds fairly rapidly even at very low temperatures.⁴⁷ It may be moderated by use of a solvent. Substitution products are formed as by-products, some saturated monochloro compounds also being obtained, apparently through cleavage of hydrogen chloride from the disubstituted halo compound, and addition of this to the original olefin:⁴⁸



The formation of substitution products may be minimized by the proper choice of conditions.

The *procedure* usually followed in chlorinating olefins is to conduct the halogen into a solution of the unsaturated compound in an inert solvent; or to add the required quantity of chlorine dissolved in carbon tetrachloride to the solution of the olefin. A previously prepared portion of the dichloro-compound may conveniently serve as a solvent for the olefin. The use of an excess of chlorine must be avoided in any case.

Compounds which are readily decomposed are best chlorinated at a low temperature. A dichloride may be obtained, for example, from α -pinene when this compound is treated with gaseous chlorine at -15 to -20° .

Bromination proceeds quite smoothly when bromine is added to a solution of the olefin in a solvent, such as carbon tetrachloride, chloroform or carbon disulfide.⁴⁹ The presence of oxygen may retard the reaction.

In the gas-phase chlorination of ethylene, the products obtained may differ according to the conditions employed. Thus, when chlorination is carried out at 300 – 350° in the presence of active carbon, hexachloroethane is obtained in 90% yield,⁵⁰ whereas at 120 – 125° in the complete absence of moisture, and using charcoal as a catalyst, dichloroethylene is obtained in 80% yield.⁵¹ Two isomeric dichlorides are obtained from cinnamic acid, depending on whether halogenation is carried out in the cold in the absence of light, or at a higher temperature and under illumination.⁴⁴⁴

In all cases of liquid-phase halogenation, a period of induction is observed which varies with the nature of the groups attached to the carbon atoms with the olefinic linkage. Activating groups generally cause a shortening of the induction period, while deactivating groups have the opposite effect. In the absence of moisture and light, the reaction is autocatalytic, oxygen functioning

as an inhibitor. *Positive* halogen appears to be the initiator of the halogenation reaction.⁴⁰²

Substitution is favored by increased olefin concentration, while increased chlorine concentration favors addition. With increasing number of chlorine atoms in the alkyl groups attached to a quaternary carbon atom, addition increases and substitution diminishes.

Addition of bromine at a double bond takes place less readily than the addition of chlorine, while iodine shows only a slight tendency toward reaction with unsaturated compounds, addition taking place with only a few olefins, such as allyl alcohol and styrene. Iodine monochloride reacts quite readily, however, giving iodochlorides.

The reaction of halogens with unsaturated compounds may be accelerated by use of catalysts.⁵² Hydrogen halides, moisture and iodine have a definite catalytic effect. (*) Light of short wave length and ultraviolet rays greatly accelerate the reaction. Aluminum chloride-metal cyanide complexes obtained by evaporating a solution of a ferrocyanide or cuprocyanide and aluminum chloride are good catalysts. Dichloroethane may be prepared in good yield by use of such a catalyst at 250°, providing the reaction is carried out in the presence of some water vapor to repress the substitution reaction.⁵³ The solvent also exerts an influence on the rate of reaction, addition of bromine to cinnamic acid, for example, taking place more readily in carbon disulfide solution than in carbon tetrachloride.⁵²

The ability of an unsaturated compound to add halogens varies according to its structure and is largely influenced by the character of groups or elements attached to the carbon atoms in the vicinity of the multiple bond. Electropositive groups such as CH₂, CH₃ etc., attached to carbon atoms with multiple bonds enhance the reactivity of the multiple bond toward halogens, while electronegative groups or atoms such as COOH, CN, Cl, etc., have the opposite effect,⁵⁴ although the high reactivity of *o*-methoxycinnamic acid,



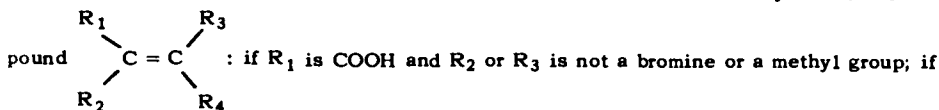
toward bromine would appear to form an exception to this rule. The rate constants for some of the olefinic hydrocarbon are as follows: ethylene 0.006, propylene 0.2, isobutylene 60, trimethylethylene 250, diisobutylene 20. These values indicate the wide variations observed in the reactivity of various olefins. *Ortho* substituents in the aryl group of aryl ethylenes (stilbenes) cause a decrease in the reactivity of the double bond.⁵⁵

Halogens do not add at ethylenic bonds between carbon atoms bearing two aromatic substituents; the group $\begin{array}{c} | \\ -\text{C} = \text{C}(\text{COOH})_2 \end{array}$ also fails to react with halogens.

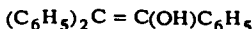
Unsaturated compounds in which the ethylenic linkage is conjugated with an aromatic

(*) It is a known fact that glass surfaces catalyze the reaction of halogens with olefins and that reaction between bromine and ethylene may be prevented by eliminating the action of the glass surface of the vessel by coating it with paraffin.

nucleus may absorb bromine only slowly; thus, cinnamic acid scarcely decolorizes bromine water unless the solution is warmed. Bromine reacts additively with the com-



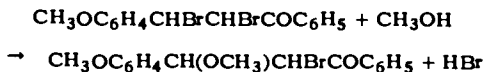
R_1 and R_3 are carboxyl groups but R_2 or R_4 is not bromine or a methyl group; if R_1 is a phenyl group and R_2 , R_3 and R_4 are all methyl groups. Addition takes place also when both R_1 and R_3 are phenyl groups and only R_2 is bromine; and when R_1 or both R_1 and R_4 are methyl groups. Stilbene, $\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5$, is converted quantitatively to the dibromide, although the reaction proceeds very slowly both in chloroform and carbon tetrachloride, and requires several days for completion. Triphenylvinyl alcohol,



is converted to diphenylbenzoyl bromomethane, $(\text{C}_6\text{H}_5)_2\text{CBrCOC}_6\text{H}_5$, when brominated in chloroform solution in the presence of phosphorus pentabromide.⁴⁴⁵

The compounds $(\text{ROCO})_2\text{C}=\text{C}(\text{COOR})_2$, $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}(\text{C}_6\text{H}_5)_2$, $\text{C}_6\text{H}_5\text{CBr}=\text{CBrC}_6\text{H}_5$, $\text{C}_6\text{H}_5\text{CCl}=\text{CClC}_6\text{H}_5$, $(\text{C}_6\text{H}_5)_2\text{C}=\text{CHBr}$, $(\text{C}_6\text{H}_5)_2\text{C}=\text{CBrCH}_3$, $\text{Cl}_3\text{C}\cdot\text{C}(\text{CH}_3)=\text{CH}_2$ and $\text{Cl}_2\text{C}=\text{CCl}_2$ do not add bromine.⁵⁶ *a-p*-Nitrophenyl-, *p*-methoxyphenyl- and *a*-phenyl-*p*-bromocinnamionitriles also fail to add bromine, while *a*-phenyl-, *a*-o-nitrophenyl-, *a*-m-nitrophenylcinnamionitrile add bromine. Cinnamionitrile and dichloroacrylic acid react with bromine with difficulty,⁵⁷ while o-methoxycinnamic acid reacts extremely rapidly. Diphenylmaleic anhydride and dimethylmaleic anhydride add chlorine but not bromine. o-Nitrocinnamic acid may be brominated by adding it to liquid bromine, or by conducting vapors of bromine through the compound. Light markedly hinders this reaction.⁴⁴⁶ Angelic acid dibromide results when *angelic acid*, $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$, is brominated in the dark, but the isomeric tiglic acid dibromide is formed when the reaction is carried out in the light.⁴⁴⁷ With certain sensitive compounds, such as allocinnamic acid, bromination may cause molecular rearrangement.⁴⁴⁸

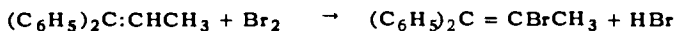
An exchange reaction occasionally takes place between the bromine of the addition compound and the solvent on heating, as in the case of dibromoanisalacetophenone and methanol:⁵⁸



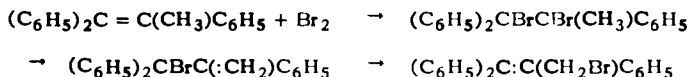
Chlorine fails to add at the double bond in isobutylene, but reacts with this compound to form methallyl chloride:⁵⁹



Similarly, bromine reacts rapidly with *gem*-diphenylpropylene to form *a*-diphenyl- β -bromopropylene:⁶⁰

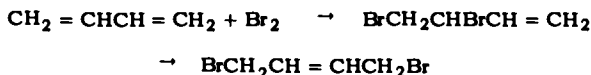


Triphenylmethylethylene also gives a substitution product with bromine:⁶¹



This type of reaction is generally limited to ethylenic hydrocarbons in which one of the unsaturated carbon atoms is fully substituted.⁶² Substitution may take place, however, at higher temperatures with other olefins; thus, propylene reacting at its boiling point with chlorine, yields allyl chloride, $\text{ClCH}_2\text{CH}=\text{CH}_2$.⁴⁴⁹

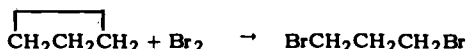
Bromine reacting with *butadiene* first gives a liquid which is apparently a 1,2-addition product; the liquid then changes to the solid 1,4-dibromo compound:⁴⁵⁰



Treatment of the latter with potassium hydroxide results in the formation of α -bromobutadiene $\text{BrCH} = \text{CHCH} = \text{CH}_2$.

When isobutylene is conducted into a solution of potassium iodide containing free iodine, trimethylcarbinol and other oxygenated compounds devoid of iodine are obtained.⁶³

Cyclopropane and other compounds of similar structure, react with bromine to form an open chain compound,



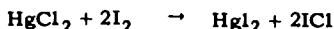
although such compounds react with chlorine to form substitution products.

Ethylene, treated with an alcoholic solution of iodine, is converted to diiodoethane.⁴⁵¹

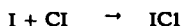
Ethylenic compounds react with iodine chloride in chloroform solution to form chloro iodo compounds:⁴⁵²



Ethylene chloriodide, $\text{ClCH}_2\text{CH}_2\text{I}$, has been obtained by conducting gaseous ethylene in an aqueous solution of iodine chloride.⁴⁵³ Iodine chloride is used for the determination of the iodine number of unsaturated fatty acids by the Hubble method. The compound is prepared by mixing solutions of mercuric chloride and iodine:⁴⁵⁴



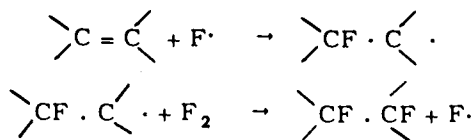
It may also be prepared by conducting a current of dry chlorine over iodine⁴⁵⁵ until the weight increase equals that calculated on the basis of the reaction:



Cyclohexene yields 1,2-dichlorocyclohexane in 90% yield by reaction with sulfuric chloride.⁴⁵⁶ The dichloride is obtained in poor yield by direct chlorination.

Addition of Fluorine to Unsaturated Compounds

Fluorine is capable of adding at the double bond of olefinic compounds, apparently by a mechanism involving atomic fluorine:



Unless special precautions are observed, however, the reaction, which proceeds with great vigor, may result in rupture of carbon to carbon bonds. Reaction may be successfully carried out at a low temperature in solution in an inert diluent, or over a metal gauze which serves to dissipate the heat of reaction rapidly.⁶⁴ Difluorodichloromethane may be used as a solvent at -78° , or

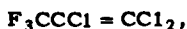
carbon tetrachloride may be employed at 0°, although it must be borne in mind that mixtures of carbon tetrachloride and fluorine are explosive and may ignite spontaneously. Carbon tetrachloride is attacked slowly by fluorine at 0°.

A noteworthy side reaction takes place when an olefin is treated with fluorine, giving rise to a compound with twice the number of carbon atoms present in the original unsaturated compound. Difluorooctachlorobutane results, for example in 20% yield, on attempted fluorination of tetrachloroethylene:



Side reactions may be eliminated to a great extent by carrying out the reaction with nascent fluorine liberated from lead tetrafluoride or iodobenzene difluoride.⁶⁵ Traces of hydrogen fluoride or silicon tetrafluoride accelerate the reaction of aryl iododifluorides with olefins.⁶⁶

Addition of fluorine at olefinic bonds has been brought about by reaction with a mixture of hydrogen fluoride and lead peroxide, PbO_2 . Trifluorotrichloropropene,



has been converted to pentafluorotrichloropropane, and tetrachloroethylene to tetrachlorodifluoroethane by this method.⁴⁵⁷

Addition of Thiocyanogen to Olefinic Bonds

Thiocyanogen, $\text{CNS}.\text{SCN}$, has the characteristics of a pseudohalogen, and, like halogens, is capable of adding at the multiple bond of unsaturated compounds. The subject has been considered in the chapter on nitriles and related compounds (Chapter 9).

Reaction of Hydrocyanic Acid with Unsaturated Compounds

Hydrocyanic acid does not, in general, react with olefinic hydrocarbons. Low yields of nitriles are obtained through reaction at 200-400° under 1000 lb pressure in the presence of metallic cobalt or copper.⁶⁷ Reaction takes place readily, however, with certain types of unsaturated compounds. Outstanding among these are the condensation products of aldehydes with compounds containing reactive methylene. For example, the unsaturated products obtained through the condensation of aldehydes with acetoacetic ester react with hydrocyanic acid in the presence of a little potassium cyanide to form saturated cyano keto esters:

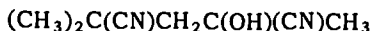


The condensation product of aldehydes with cyanoacetic ester, malonic ester, malononitrile, and benzyl cyanide react similarly.⁶⁸

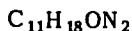
Many of the unsaturated compounds resulting from the condensation of carbonyl compounds among themselves are also capable of reacting with hydrocyanic acid. *Benzalacetophenone*, for example, reacting with hydrocyanic acid generated *in situ* by the addition of acetic acid to a solution of potassium cyanide, gives α -phenyl- β -benzoylpropionitrile:⁶⁹



Both the carbonyl and the unsaturated bonds in *mesityl oxide* being reactive, this compound yields a saturated cyanocyanhydrin,

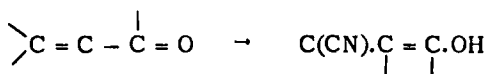


by reaction with hydrocyanic acid.⁷⁰ *Phorone* gives a cyanocyanhydrin,



when heated at 100° with hydrocyanic acid in the presence of a little potassium cyanide.⁷¹ Reacting with one molecular proportion of hydrocyanic acid at 10-40° *vinyl ethyl ketone* gives levulinic nitrile, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CN}$.⁷²

Carbonyl compounds in which an unsaturated bond is present in 2,3-position may react with hydrocyanic acid to form the 3-cyano substituted enolic compound by 1,4-addition:



The reactivity of the unsaturated bond, in all these compounds is induced by the electronegative groups attached to the unsaturated carbon atom. Other classes of compounds in which a negative group is attached to an unsaturated carbon atom show reactivity toward hydrocyanic acid. *ω-Nitrostyrene*, for example, reacts with a molecule of hydrocyanic acid to form a cyanonitrophenylethylene. Nitrocamphene reacts in a similar manner.⁷³ *α-Nitroolefins* such as *α-nitrobutene* are capable of adding hydrocyanic acid to form *β-* and *γ-nitronitriles*. Addition takes place with *α,β-unsaturated acids*, in general, their esters, *α,β-unsaturated nitriles* and ketones, and results in the formation of saturated *β-cyano derivatives*.⁷⁴

Hydrocyanic acid may be made to react almost quantitatively with *acrylonitrile*, in the presence of a little potassium cyanide to form succinonitrile:⁷⁵



Cyanoacrylates also react with hydrocyanic acid in the presence of cyanide ions.⁷⁶ Hydrocyanic acid also adds at the double bond in *isocrotonic acid* to give *β-cyanobutyric acid*. The reaction is accelerated by primary or secondary amines.⁷⁷ The reactivity of the double bond in *unsym-diphenylethylene* may be ascribed to the negative phenyl groups attached to the unsaturated carbon atom.⁷⁸

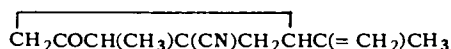
α-Phenyl-p- and *α-phenyl-o-nitrocinnamonnitrile* do not fix hydrocyanic acid, while the corresponding *α-phenyl-m-nitro* isomer reacts with a molecule of hydrocyanic acid.⁷⁹

Vinyl acetate reacting with hydrocyanic acid gives cyanoethyl acetate,

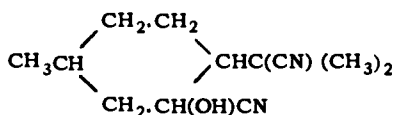


and *vinyl ethyl ketone* gives a cyano cyanhydrin, $\text{CNCH}_2\text{CH}_2\text{C}(\text{OH})(\text{CN})\text{C}_2\text{H}_5$.⁸⁰

Carvone reacts with hydrocyanic acid to form a cyanohydrocarvone,



and a cyanohydrocarvone cyanhydrin. *Pulegon* reacting with one mole of hydrocyanic acid gives a cyclic amide, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{C} \begin{array}{c} \text{---} \text{C}(\text{CH}_3)_2 \text{CONH} \end{array}$, and a cyanocyanhydrin,



with two molecules of hydrocyanic acid.⁸¹

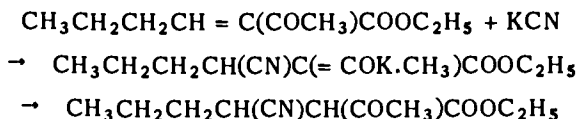
Acetylene reacts readily at 75° with hydrocyanic acid in a concentrated aqueous solution of cuprous chloride and ammonium chloride acidified with hydrochloric acid, to form acrylonitrile.⁸² Acetylene should be used in slight excess, the solution should contain 650 gm of cuprous chloride per lit. and the CuCl and NH_4Cl should be present in a ratio of 1:0:8. The liquid should react acid to congo red (pH 3.5), the acidity being maintained by the continuous or intermittent addition of the required amount of hydrochloric acid. The presence of mercury salts is claimed to increase the yields.⁸³ The process has been employed on the commercial scale with the production of 18-30 gm acrylonitrile per hour per liter of catalyst solution, with yields ranging 75 to 87% of the theoretical. Small amounts of acetaldehyde, acetaldehyde cyanhydrin, vinylacetylene, divinylacetylene, chloroprene, 1-cyanobutadiene and some resinous matter are formed as byproducts in the process.

The crude nitrile obtained is subjected to a process of purification; it is largely freed of acetylene polymers by washing with water.⁸⁴ Acetaldehyde and divinylacetylene may be eliminated by careful azeotropic distillation with methanol or water.⁸⁵ Passing a stream of acetylene or an inert gas through the crude nitrile maintained at 50°⁸⁶ and treatment with a small amount of chlorine⁸⁷ are also claimed to remove these impurities effectively.

Propiolic acid esters react with hydrocyanic acid to form β -cyanoacrylic esters.⁸⁸

Reaction of Olefins with Potassium Cyanide

Many unsaturated compounds that show reactivity toward hydrocyanic acid are also capable of reacting with potassium cyanide. Reaction takes place, for example, with condensation products of aldehydes and compounds containing a reactive methylene. Thus, *butylidene acetoacetate* reacts with potassium cyanide to form cyanobutyleneacetoacetate, a 1,4-addition product with the cyanide being apparently formed as an intermediate.⁸⁹



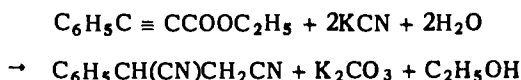
Similar reactions take place with diethyl ethylidenemalonate, benzal malonic methyl ester, furfurylidene malonic ester, cinnamylidenemalonic ester and α -phenyl cinnamionitrile.⁹⁰ Alkylidene and arylidene cyanoacetates react similarly.⁹¹

Condensation takes place with *benzylidenecyanoacetic acid* between the unreacted

acid and the addition product to form a tricyano compound which is converted on boiling to $\text{C}_6\text{H}_5\text{CH}(\text{CN})\text{CH}(\text{CN})\text{CH}(\text{C}_6\text{H}_5)\text{CH}_2\text{CN}$.⁹²

Potassium cyanide reacts with *methyl fumarate* giving a 1,4-addition product, which condenses with a molecule of fumaric ester, forming a cyclopentanone derivative. With *methyl citraconate* a cyclic nitrogen compound is formed.⁹³ *Allyl cyanide* reacts with potassium cyanide to form pyrotartaric dinitrile.

The reaction of potassium cyanide with *ethyl phenylpropiolate* results in the formation of monophenylsuccinonitrile⁹⁴

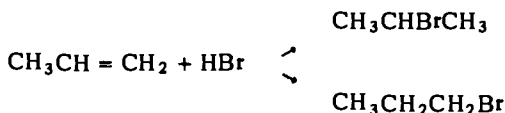


Addition of Hydrogen Halides to Olefins – Markownikow's Rule

Hydrogen halides react more or less readily with unsaturated compounds to form monohalo compounds:



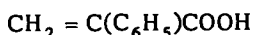
The halogen attaches itself to the carbon atom combined with the fewest hydrogen atoms. This generalization, which is known as *Markownikow's rule*,⁹⁵ does not always hold strictly. In some instances the normal substitution proceeds partially, and addition in the reverse direction also takes place simultaneously.⁹⁶ Thus, the reaction of hydrogen bromide with propylene results in the formation of both the 1- and 2-bromo propanes:



the 2-bromo compound forming the major product. The reaction is often one of equilibrium, the olefin and the halogenated product being both found in the final reaction mixture.⁴⁵⁸ The use of acetic acid as a solvent favors the abnormal

reaction. Divinylpiperazine, $\text{CH}_2 = \text{CHCHNHCOCH}(\text{CH} = \text{CH}_2)\text{NHCO}$, adds halo acids readily in the direction contrary to the rule.⁹⁶ Dry hydrogen bromide reacting with allyl bromide, $\text{CH}_2 = \text{CHCH}_2\text{Br}$, gives principally 1,3-dibromopropane, $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}$, while in the presence of a solvent, or with moist hydrogen bromide, propylene bromide, $\text{CH}_3\text{CHBrCH}_2\text{Br}$ is formed.

The temperature may also exert an influence on the course of the reaction. A striking example is presented by the behavior of atropic acid,



which is converted to α -bromoatropic acid when it is subjected to the action of hydrogen bromide at 0° , while if the reaction is carried out at 100° , the β -bromo acid is formed.⁴⁶⁰

The normal reaction may be considered the result of the attack of a positive halogen ion on the positive carbon atom, following the addition of a proton to the negative atom.

Ortho and *para* directing groups promote the addition of halogen acids in accordance with Markownikow's rule, and the reverse action is manifested by *meta* directing groups, according to a generalization advanced by Robinson.⁹⁷

The chlorides of iron, cobalt, nickel and aluminum facilitate the addition of hydrogen halides to olefins.⁴⁶¹ The reaction of dichloroethylene and trichloroethylene with hydrogen chloride takes place at 30 to 40° in the presence of aluminum chloride, the former giving 1,1,2-trichloroethane, the latter, 1,1,1,2-tetrachloroethane.⁴⁶²

Hydrogen iodide reacts with olefins most readily and hydrogen chloride least readily, hydrogen bromide occupying an intermediate position. Gaseous ethylene is not absorbed by concentrated hydrochloric acid, but reacts readily with hydrobromic and hydriodic acids.

A satisfactory procedure in carrying out the reaction of hydrogen halides with unsaturated compounds is to add the latter to a concentrated solution of the hydrogen halide in water or in glacial acetic acid, allowing the mixture to stand until reaction is complete. The reaction may be accelerated by heating in a closed vessel under pressure.⁹⁸

Acetic acid solutions of hydrogen chloride give particularly good results with compounds of the terpene and sesquiterpene series, with which crystalline chlorides are difficult to obtain. In order to assure good results, the reaction mixture is saturated with the hydrogen halide, and is allowed to stand two or three days in a cool, dark place.

In carrying out the reaction with hydrogen bromide, the purified olefin is dissolved in benzene, hexane or a light petroleum fraction freed from olefins, an antioxidant is added, air is swept out with hydrogen and then gaseous hydrogen bromide free from air is passed through the solution. The reaction is usually carried out at 0° to 20°. The use of an antioxidant can be dispensed with if acetic acid is used as a solvent. Acetic acid, catechol, quinol, thiophenol, diphenylamine or hydrogen may be employed as antioxidants.

The addition of hydrogen halides to double bonds in terpenes often proceeds with a rearrangement in the ring system. Unstable carbon ring structures are often ruptured under the action of hydrogen halides. Pinene in acetic acid solution gives mainly dipentene dihydrochloride with rupture of the bridged or cyclobutane ring.

The ease of reaction of an unsaturated compound with hydrogen halides depends upon its structure. Straight chain olefinic hydrocarbons generally fail to combine with hydrogen chloride at room temperature, though reactivity increases somewhat with increasing molecular weight, and the higher olefins react with some ease with hydrogen chloride. In general, terminal double bonds add hydrogen halides with greater difficulty than those removed from the end of the chain by one or more carbon atoms, this fact making possible the separation of an olefin with a terminal double bond from its isomers. Addition would seem to proceed with greater difficulty, the greater the number of hydrogen atoms attached to the unsaturated carbon atom. Thus, while hydrocarbons of

type $\text{CH}_2 = \text{CRR}'$ and $\text{RCH} = \text{CR}'\text{R}''$ add hydrogen chloride in the cold, the simple alkylated ethylenes $\text{CH}_2 = \text{CHR}$ react only on heating.

Unsaturated compounds in which two carbon atoms are attached to the unsaturated carbon react rapidly with hydrogen chloride in the absence of a catalyst, whereas those in which only one carbon atom is attached to the unsaturated carbon react only in the presence of a catalyst, such as aluminum chloride.⁹⁹ Thus, trimethylethylene, $(\text{CH}_3)_2\text{C} = \text{CHCH}_3$, combines readily with hydrogen chloride while the isomeric amylenes are unreactive in the cold and in the absence of a catalyst.

Halogenated olefins add hydrogen halides less readily than the corresponding unsaturated hydrocarbons.¹⁰⁰

Propylene yields a very small quantity of normal propyl iodide with hydriodic acid,¹⁰¹ while isobutylene reacting with hydrogen bromide in acetic acid solution gives 93% of *tert*-butyl bromide and 7% of isobutyl bromide although primary isobutyl bromide is formed when bromination is carried out in 40% hydrobromic acid solution.¹⁰² Olefins of the type $\text{CH}_3\text{CH} = \text{CHCH}_2\text{R}$ reacting with hydrogen bromide give equal amounts of the two possible isomeric saturated bromides.¹⁰³ Allyl bromide $\text{BrCH} = \text{CHCH}_3$ reacting with hydrogen halides gives 35% of the 1,1- and 65% of the 1,2-halo product.

Hydrogen chloride adds to *butadiene* to give 3-chloro- Δ^1 -butene, $\text{CH}_2 = \text{CHCHClCH}_3$ in 75-80% yield, together with 20 to 25% yield of 1-chloro- Δ^2 -butene, $\text{CH}_3\text{CH} = \text{CHCH}_2\text{Cl}$. Hydrogen bromide reacting in the presence of antioxidants gives the 1,2-addition product in 80-90% yield, together with 10-20% yield of crotyl bromide. At a high temperature and especially in the presence of oxygen, the 1,2-addition product isomerizes to crotyl bromide.

Vinylacetylene reacts with aqueous hydrogen chloride at 20° to give a 1,4-addition product:¹⁰⁴



Of the isomeric brominated olefins $\text{RCBr} = \text{CH}_2$ and $\text{RCH} = \text{CHBr}$, the former reacts much more readily with hydrogen halides than the latter, thus making possible the separation of isomeric halo olefins of this type. β -Bromostyrene adds hydrogen bromide very rapidly to form β,β -dibromoethylbenzene, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{Br}_2$.⁴⁰³

Hydrogen iodide adds to methylethylethylene, $\text{CH}_3\text{CH} = \text{CHC}_2\text{H}_5$, giving 2-iodopentane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHICH}_3$.¹⁰⁵

Hydrogen chloride adds to the double bond of 1,1,1-trichloro-2-pentene, $\text{Cl}_3\text{CCH} = \text{CH}_2$, to form 1,1,1,2-tetrachloropropane, $\text{Cl}_3\text{CCHClCH}_3$, while the double bond in 1,1,1-trichloro-2-methyl-2-propene, $\text{Cl}_3\text{CC}(\text{CH}_3) = \text{CH}_2$ is quite inert.¹⁰⁶

Allylamine and diethylallylamine react with hydrogen chloride to form the 2- and 3-chloro isomers in about equal quantities; triethylallylammmonium chloride gives over 83% of 3-chloropropyltriethylammmonium chloride. Hydrogen bromide reacting with triethylallylammmonium chloride in the absence of peroxides gives the 2-bromopropylidimethyl ammonium salt and the 3-bromo isomer in a total of 60% yield.¹⁰⁷

Vinyl ethers react with hydrogen chloride to form a compound, CH_3CHClOR , with a reactive chlorine readily replaceable by negative groups. The reaction of dichlorovinyl ethyl ether, $\text{ClCH} = \text{CClOC}_2\text{H}_5$, with hydrogen chloride leads to the formation of the trichloroethyl ether, $\text{ClCH}_2\text{CCl}_2\text{OC}_2\text{H}_5$. When the latter is heated it decomposes to chloroacetyl chloride and ethyl chloride.⁴⁶³

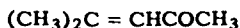
The reaction of hydrogen halides with α,β -unsaturated acids and ketones results, as a rule, in the formation of the saturated β -halo acids or ketones, while reaction with β,γ - and γ,δ -unsaturated acids gives the γ -halo acids.¹⁰⁸

Acrylic acid presents an exception and gives the α -bromo product



with bromine.

The reaction of hydrogen halides with unsaturated ketones proceeds in a complicated manner and results in the formation of colored isomers of the normal addition product, and complexes containing several hydrogen halide molecules.¹⁰⁹ Mesityl oxide,



has been converted to the bromoketone, $(\text{CH}_3)_2\text{CBrCH}_2\text{COCH}_3$, by treatment with gaseous hydrogen bromide at a low temperature.⁴⁶⁴

Nitro olefins reacting with hydrogen halides give halo nitro paraffins:



Reaction in the Presence of Catalysts

While ethylene and hydrogen chloride do not react even when the mixture of these gases is heated to a high temperature, combination takes place readily above 100° in the presence of aluminum chloride and halides of certain other metals.¹¹⁰ The reaction of other olefin hydrocarbons with hydrogen chloride may be similarly accelerated by catalysts; thus, propylene reacts with hydrogen chloride in the presence of aluminum chloride supported on silica gel to form isopropyl chloride in 97% yield.¹¹¹ Tertiary amines also accelerate the normal addition of hydrogen chloride to unsaturated compounds.¹⁰⁷ The reaction of hydrogen iodide with allyl bromide is accelerated by peroxides.¹¹²

The reaction of *ethylene* and hydrogen chloride at -78° in solution in ethyl chloride and in the presence of aluminum chloride results in the formation of ethyl chloride in 99.7% yield. Ethyl bromide can also be prepared in a similar manner.¹¹³ Good yields of the halogenated compound may be obtained at higher temperatures, but polymeric products form in increasing amount with rise in temperature. The use of higher boiling solvents, such as trichlorethylene, makes possible the removal of the chloro compound formed by allowing the temperature to rise to $20-60^\circ$ by the heat of reaction.¹¹⁴

Abnormal Addition of Hydrogen Bromide – The Peroxide Effect

Hydrogen bromide may add to olefinic hydrocarbons in a direction opposite to that predicted by Markownikow's rule, if the reaction is carried out in the presence of a peroxide.¹¹⁵ This directing influence may be manifested also, in some cases, by atmospheric air or oxygen. The degree in which peroxides thus affect the course of the reaction of hydrogen bromide with a given unsaturated compound seems to depend to a great extent on the nature of the latter.

The abnormal reaction is apparently the result of the action of free radicals giving rise to atomic bromine, which attacks the carbon atom having the higher electron density. This results in the formation of an organic radical, which in turn reacts with hydrobromic acid to regenerate a bromine atom:¹¹⁶



the reaction thus proceeding by a chain mechanism. The reaction is initiated by the peroxide present, through its dissociation into a free radical and the interaction of the latter with hydrogen bromide, giving rise to bromine atoms.

Abnormal addition is not observed with hydrogen chloride, iodide and fluoride.¹¹⁷

The peroxide-induced abnormal addition of hydrogen bromide may be carried out in benzene solution, or in hexane or carbon disulfide solution. The air is not removed from the stream of hydrogen bromide, and the solution is preferably illuminated with a powerful electric light, although the use of this latter device is not essential. Dilution of the solution of the olefin and higher temperatures favor the abnormal reaction.

Benzoyl peroxide or lauroyl peroxide are satisfactory reagents to induce the abnormal addition; perbenzoic acid, ascaridole and α -heptenylheptaldehyde have also been used for the purpose. Three moles of peroxide should be present to every hundred moles of the olefin. Oxygen and air alone may induce the abnormal reaction in some instances. Peroxides in themselves are ineffective in bringing about the abnormal reaction if acetic acid is employed as a solvent and the reaction is carried out in the absence of oxygen.¹¹⁸

The abnormal reaction proceeds quite readily, in some instances, under the action of atmospheric oxygen and diffuse sunlight alone. 11-Bromoundecanoic acid is formed rapidly, for example, in over 90% yield, when hydrogen bromide mixed with air is passed through a 10% solution of Δ^{10} -undecenoic acid in benzene or hexane exposed to diffuse sunlight. The highly purified unsaturated acid in hexane solution treated in a similar manner gives only the normal addition product, although the presence of only a trace of peroxide induces the abnormal reaction.¹¹⁹

Some olefins, such as vinyl bromide and allyl bromide, are highly sensitive to peroxides, whereas others, e.g., butene-1, are comparatively insensitive. The nature of the solvent, the temperature and other external conditions may exert a marked influence on the course of the reaction with unsaturated bodies that are sensitive to peroxides.

The terminal double bond in compounds of the type $\text{CH}_2 = \text{CHCH}_2\text{X}$ will take up hydrogen bromide in the abnormal manner giving



provided that X is not itself, or does not contain a strongly antioxidant group such as CH_2OH . Thus, undecenyl acetate, $\text{CH}_2 = \text{CH}(\text{CH}_2)_8\text{CH}_2\text{OCOCH}_3$, and allylbenzene readily give the ω -bromo compounds in 90% yield. The abnormal product may be obtained from styrene by reaction with hydrobromic acid at 95° in benzene solution in the presence of benzoyl peroxide. Acrylic acid gives only the normal product $\text{CH}_2\text{CHBrCOOH}$, although the carboxyl group exerts only slight effect in the higher olefinic acids, $\text{CH}_2 = \text{CH}(\text{CH}_2)_n\text{COOH}$, and the abnormal product may be obtained from these by carrying out the reaction in the presence of peroxides.

Hydrogen bromide reacts with isoprene at 0° to form the *tert*-bromide



but this compound slowly undergoes rearrangement at ordinary temperature to the isomeric primary bromide $(\text{CH}_3)_2\text{C} = \text{CHCH}_2\text{Br}$.⁴⁶⁵ A rearrangement of this type has been observed with unsaturated bromo compounds $\text{RCHBrCH} = \text{CH}_2$, and



The effect of alkyl groups would appear to be more or less equivalent, and about equal proportions of the isomeric brominated compounds are obtained regardless of whether the reaction is carried out in the presence or absence of peroxides.¹²⁰

The "peroxide effect" seems to be absent in the gas phase reaction of hydrogen bromide with olefins.¹²¹

Addition of Hydrogen Fluoride to Unsaturated Compounds

Hydrogen fluoride adds at olefinic double bonds with great ease. It reacts readily with ethylene, propylene and cyclohexene without the use of a catalyst. Hydrogen fluoride in the anhydrous condition is suitable for the purpose. The reaction proceeds more readily with the higher olefins than with the lower members of the series.¹²² Addition takes place in accordance with Markownikow's rule.

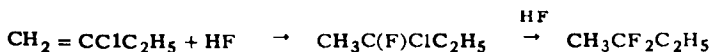
Polymerization of olefinic compounds also takes place under the action of hydrogen fluoride, and at an increasing rate with rising temperature. For that reason, the reaction is best carried out at a low temperature. When the olefin contains a halogen attached to one unsaturated carbon atom, addition proceeds smoothly, and there is little tendency toward polymerization.⁴⁶⁷ The reaction of hydrogen fluoride with ethylene proceeds at a good rate only at 90°, but many homologs of ethylene react at an appreciable rate at 0° or even at a lower temperature. Fluorides have been obtained from ethylene in 82% yield, from propylene in 62% yield, and cyclohexene¹²³ in 80% yield. Olefins other than ethylene give a secondary or tertiary fluoride. In the presence of acids, these tend to decompose, giving olefins which may then polymerize.⁴⁶⁸

Hydrogen fluoride reacts with cyclopropane causing rupture of the ring and giving *n*-propyl fluoride in 80% yield.¹²⁴

Unsaturated acids react with hydrogen fluoride at 10° or at a somewhat higher temperature to give saturated fluorinated acids.¹²⁵

It is claimed that olefins in which an oxygen atom is attached to a carbon atom in the immediate vicinity of the double bond, such as allyl alcohol or cinnamic acid, generally fail to react with hydrogen fluoride or to polymerize under the action of this compound.¹²⁶

Halo olefins of the type $\text{RCH} = \text{CHX}$ fail to react at room temperature, and react poorly at higher temperatures with hydrogen fluoride, to give impure products. Compounds of the type $\text{RR}'\text{C} = \text{CHX}$ react readily, on the other hand, at temperatures in the range -23 to 0°, with the formation of only negligible amounts of tarry matter. Thus, both isocrotyl and methallyl chlorides give 1-chloro-1-fluoro-2-methylpropane in good yield,¹²⁴ the latter after undergoing molecular rearrangement. Halogenated olefins of the type $\text{R}'\text{R}''\text{C} = \text{CXR}$ react with extreme rapidity with hydrogen fluoride at low temperatures;¹²⁷ hydrogen fluoride also causes the replacement of chlorine by fluorine:



and the liberated hydrogen chloride reacts with the unreacted chloro olefin to form a dichloro compound. Asymmetrical dihalo olefins $\text{RR}'\text{C} = \text{CX}_2$ combine smoothly with hydrogen fluoride at 65°, with little substitution. 1,1-Dichloroethylene, reacting with four moles of hydrogen fluoride, gives 1,1-dichloro-1-fluoroethane in 50% yield.¹²⁸ At elevated temperatures tar formation becomes the dominant reaction. Symmetrical di-

halo olefins, $RCX = CXR'$, give inconsistent results:⁴⁶⁹ 1,2-dichloroethylene fails to react with hydrogen fluoride, while *cis*- and *trans*-1,2-dichloro-1-propene react smoothly at 120° to form $CH_3CFCICH_2Cl$ and some substitution product. 1,2-Dichloro-2-propene reacting with hydrogen fluoride gives 1,2-dichloro-2-fluoropropane, $CH_3CFCICH_2Cl$, with little substitution product.¹²⁹

Hydrogen fluoride reacts vigorously with ketene in inert solvents or in the vapor phase to form acetyl fluoride:¹³⁰



Only polymeric products result if the temperature is allowed to rise excessively.

The reaction of carbon monoxide with hydrogen fluoride in the presence of formaldehyde at 160° and under 750 atm pressure results in the formation of fluoracetic acid:¹³¹



Equivalent quantities of hydrogen fluoride and formaldehyde and an excess of carbon monoxide are employed, and water is carefully excluded from the reaction mixture.

Reaction of Hydrogen Fluoride with Acetylenic Compounds

Acetylene under pressure, kept in contact with hydrogen fluoride at room temperature for a long period, reacts to form vinyl fluoride. Substituted acetylenes react rapidly with hydrogen fluoride, even at -70°, forming only saturated difluoro compounds. No monomeric addition product has been obtained with vinylacetylene.

A satisfactory *procedure*¹³² is to pass vapors of the acetylenic compound into anhydrous liquid hydrogen fluoride in a copper flask cooled in ice. The acid is used in 25% excess. After allowing an hour for the completion of the reaction, the volatile constituents of the reaction mixture are evaporated off and the residue is poured on ice, the oily matter is collected and the fluorinated compound is isolated by distillation. Yields generally average about 75% of theoretical.

The liquefied hydrocarbons may be added dropwise to hydrogen fluoride cooled to a sufficiently low temperature, the mixture being then allowed to warm up to room temperature. The reaction is best carried out with hydrofluoric acid in solution in ether or a ketone, the latter being used in connection with higher boiling alkynes. Yields with the latter compound approach 90%.

The reaction has also been carried out in the gas phase by using a catalyst consisting of mercury oxide or halide precipitated on charcoal.¹³³ The reaction is exothermic and it is necessary, in some cases, to dilute the mixture of acetylenic compound and hydrogen fluoride with an inert gas or the vapors of methylene chloride or carbon tetrachloride in order to bring it under control. Vinyl fluoride has been obtained in good yield by passing an equimolecular mixture of acetylene and hydrogen fluoride over carbon pellets impregnated with a mixture of mercuric chloride and barium chloride and heated at 100°.¹³⁴

The reaction of hydrogen fluoride with compounds having more than one acetylenic linkage may take a complicated course. The reaction of 1,8-nona-

diyne in an oxygenated solvent leads to the formation of a mixture of 2,8-difluoronona-1,8-diene and 2,2,8,8-tetrafluorononane. The reaction may also result in the polymerization of the acetylenic compound, as is the case with 1,6-heptadiyne.

Addition of Hypohalous Acids to Olefins

Hypohalous acids XOH add at the unsaturated bonds of olefinic compounds to form halohydrins, the hydroxyl group becoming attached to the carbon atom with the least number of hydrogen atoms:¹³⁵



No regularity has been observed in the direction of addition of hypochlorous acid to unsaturated acids, and both isomeric forms are often obtained simultaneously. Some dichlorides are frequently formed because of the instability of hypochlorous acid that results in release of chlorine. Dichlorides are formed in increasing proportion with increasing molecular weight of the olefin.

The reaction with hypochlorous acid is carried out by allowing the olefin to remain in contact with a dilute solution of hypochlorous acid for a prolonged period.¹³⁶ Styrene chlorohydrin is obtained in poor yield by the direct action of hypochlorous acid on styrene, but has been obtained in good yield by reaction with acid liberated by the action of carbon dioxide on calcium hypochlorite.¹³⁷

Chlorohydrins of unsaturated compounds insoluble in water may be prepared by use of an ethereal solution of hypochlorous acid, which may be obtained by extracting the aqueous solution of the acid with ether,¹³⁹ although the preparation of large quantities of the ethereal solution is a laborious process, and the solution is unstable even at a low temperature. A more satisfactory procedure is to make use of the ethyl ester of hypochlorous acid in solution in carbon tetrachloride. The ester reacts directly with the unsaturated compound, or reacts after decomposition into alcohol and the free hypochlorous acid.¹⁴⁰

A solution of sodium hypochlorite in aqueous sodium carbonate or bicarbonate has been employed for the preparation of amylene chlorohydrins.¹⁴¹

Sodium fumarate or maleate reacting with chlorine water give monochloromaleic acid; $HOCOCHClCH(OH)COOH$; reaction with bromine water proceeds in the same manner. Since the formation of hypochlorous acid from chlorine and water is depressed by neutral chlorides in solution,¹⁴² the reaction of fumaric acid with chlorine in solution in water containing a high concentration of chlorides result in the formation of dichlorosuccinic acid.

Glycerine dichlorohydrin, $ClCH_2CHClCH_2OH$, is obtained by conducting chlorine through a solution of allyl chloride in water.¹⁴³

tert-Butyl hypochlorite in acetic acid solution reacts with styrene to form the *tert*-butyl ether of the chlorohydrin in 84% yield.¹⁴⁴



Chlorohydrins are formed in 35 to 50% yield through the interaction of 1-olefins and chromyl chloride, CrO_2Cl_2 , and subsequent hydrolysis of the complex formed.⁴⁷⁰ The hydroxyl group takes the primary position in $RCH = CH_2$ giving $RCHClCH_2OH$, while reaction with hypochlorous acid yields the isomeric secondary halo alcohol,



The reaction has been successfully applied to olefins with three to six carbon atoms.

Diisobutylene gives principally an unsaturated chloride when treated with hypochlorous acid.

Cyclic unsaturated compounds react in a normal manner, as a rule, and chlorohydrins have been obtained from cyclopentene, cyclohexene, cyclooctene and camphene.⁴⁷¹ α -Pinene reacts with rupture of the bridge ring with the formation of three dichlorohydrins.⁴⁷²

Bromohydrins may be prepared by simply agitating the olefin with a dilute aqueous solution of bromine, while the latter is continually replenished as it is consumed in the reaction.⁴⁷³ A bromoether results when the reaction is carried out in alcoholic solution. When bromine water is made to react with fumaric or maleic acids in the presence of much sodium bromide, dibromosuccinic acid results.

When weak acids such as boric or carbonic acids are employed to decompose sodium hypobromite in aqueous solution, hypobromous acid is released, while strong acids cause the formation of bromine.

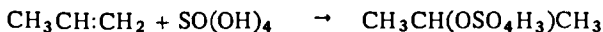
Iodohydrins are obtained by allowing the theoretically required quantity of iodine to react with the unsaturated compound in moist ethereal solution in the presence of mercuric oxide. The ether must be free from alcohol. The iodoacetate may be obtained readily by carrying out the reaction in the presence of acetic anhydride.¹³⁸

Addition of Sulfuric Acid, Bisulfites, Sulfur Dioxide and other Sulfur Compounds

Unsaturated compounds are capable of reacting with sulfuric acid to yield addition compounds, among which are found esters of sulfuric acid. These esters are formed through the addition of sulfuric acid at the multiple bond, addition taking place in accordance with Markownikow's rule, i.e., the acidic group combining with the carbon atom to which fewest atoms of hydrogen are attached:



Dialkyl sulfates may be formed with more concentrated sulfuric acid. Sulfuric esters are not the only product, nor even the principal product, of the reaction of sulfuric acid with unsaturated compounds. Another addition reaction also takes place, apparently one between the true monohydrate of sulfuric acid and the olefin, resulting in the formation of an ester of orthosulfuric acid:



Thus, when amylenes, hexenes or heptenes are dissolved in sulfuric acid, and the clear, homogeneous solutions obtained are diluted with water cooled to 0°, the free alcohols are precipitated in yields approaching 70% of theory. This fact cannot be accounted for on the assumption that sulfuric esters are formed and are hydrolyzed when the liquid is diluted with water, since the acid sulfuric esters of the alcohols in question are known to be unaffected by water in the cold and are hydrolyzed slowly even at 100°. That sulfuric esters are formed in the reaction is shown by the fact that they may be isolated, in the form of their barium salts, from the aqueous layer after the al-

cohols have been eliminated by extraction with an organic solvent. Resistance to hydrolysis is shown also by ethyl acid sulfate, which is decomposed only to the extent of 16% when heated with water at 60° for eight days.¹⁴⁵

It is significant also that in the reaction with olefins, the highest yields of alcohol are obtained with sulfuric acid containing water. Thus, a greater yield of alcohol is obtained when an 85% sulfuric acid is used than when a 95% or 100% acid is employed.

Use of a deficiency of sulfuric acid may be expected to favor the formation of neutral esters, while an excess of acid should favor the formation of the acid ester.

Olefins with three or more carbon atoms reacting with 90 to 93% sulfuric acid give alkyl sulfates and unsaturated polymeric bodies. Sulfuric acid of 98% strength reacting with such hydrocarbons at 20° or at lower temperatures causes the formation of some saturated hydrocarbons which precipitate out; on dilution of the solution with water, a mixture of unsaturated compounds separates. Treatment of dodecene-1 with sulfuric acid results in the formation of the 2-sulfate, together with smaller amounts of the 3-, 4-, and 5-sulfates.⁴⁷⁴

The tendency of olefins to react with sulfuric acid is distinctly less marked than their ability to combine with bromine, for example. The rate of reaction is governed by the character of the groups in the vicinity of the multiple bond. An accumulation of negative groups exerts a retarding effect on the reaction, while electropositive substituents, such as methyl groups, increase the reactivity of unsaturated compounds. Thus, isobutylene, $(\text{CH}_3)_2\text{C} = \text{CH}_2$ is rapidly and completely dissolved by sulfuric acid of 63% H_2SO_4 content at 17°, and tetramethylethylene reacts readily and completely with 77% acid at room temperature. The rate of reaction with the methylethylenes decreases in the order *unsym*-dimethylethylene, trimethylethylene, tetramethylethylene. Butylene $\text{C}_2\text{H}_5\text{CH} = \text{CH}_2$ is less readily acted upon than *unsym*-dimethylethylene.

The tendency to yield alcohols and sulfuric esters reaches a maximum with amylenes and hexenes, polymerization assuming significant proportions with the higher olefins.

Ethylene reacts with sulfuric acid at 70° to form ethyl hydrogen sulfate; butylenes dissolve in 80% sulfuric acid and in concentrated sulfuric acid, but undergo extensive polymerization in the latter. Cinnamic and fumaric acids and dichloroethylene are comparatively unreactive toward sulfuric acid.

Fuming sulfuric acid readily absorbs the lower alkylenes, ethylene giving carbonyl sulfate anhydride, $\overline{\text{CH}_2\text{CH}_2\text{SO}_2\text{OSO}_2\text{O}}$.

Reaction of Unsaturated Compounds with Bisulfites

Unsaturated hydrocarbons do not add bisulfites as a rule, in the absence of oxygen, although a fairly rapid reaction takes place in the presence of large volumes of oxygen with 2-normal ammonium bisulfite solution in the pH range 5 to 6. Addition takes place in an abnormal manner, i.e., contrary to Markownikow's rule:¹⁴⁶



The reaction is rarely complete, ethylene giving a 12% yield of the sulfonate, propylene 55%, isobutylene 62%. Styrene yields three distinct products,



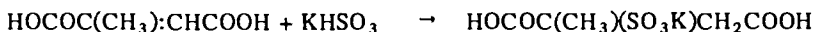
the last forming more than 50% of the total sulfonates.¹⁴⁷

The reaction of sulfurous acid or sodium bisulfite with amylene, cyclohexene, trimethylethylene and dipentene proceeds readily.¹⁴⁸ Pinene and 2,4,4-trimethyl-2-pentene give 15 to 20% yields of the sulfonate.

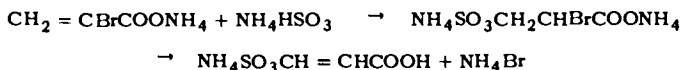
Unsaturated alcohols related to terpenes add sodium bisulfite forming water-soluble sulfonates. Thus, linalool and geraniol are completely dissolved on shaking with aqueous sodium bisulfite. Citral also reacts readily with the compound.

Nitro olefins react with sodium bisulfite to form sodium-1-nitro alkane-2-sulfonates, which on reduction with hydrogen in the presence of Raney nickel give the corresponding amino sulfonic acids.

Unsaturated fatty acids react readily with sodium bisulfite to form sulfonates of the corresponding saturated fatty acids. When the double bond is in the α,β -position, β -sulfonic acids always result. Thus, β -sulfobutyric acid is obtained from crotonic acid.¹⁴⁹ Similarly cinnamic and tropic acids add bisulfite to yield β -sulfonic acids.¹⁵⁰ Maleic acid adds bisulfite, reaction taking place more readily than with fumaric acid.¹⁵¹ The acid salts of fumaric acid react more readily with bisulfites than the neutral salts, while the reverse is true of maleic acid. Potassium sulfomethylsuccinic acid results in excellent yield through the reaction of citraconic acid with potassium bisulfite:¹⁵²



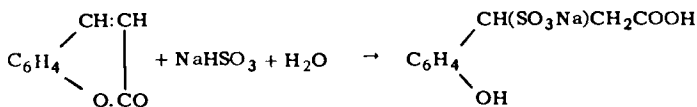
A number of unsaturated halo acids react additively with a molecule of bisulfite and subsequently lose the elements of hydrogen halide to give an unsaturated sulfonic acid.¹⁵³



Trans- β -chloroacrylic acid yields *cis*- β -sulfoacrylic acid, while the *cis*-chloro acid gives the *trans*-sulfo acid. The former, treated with concentrated sulfuric, is converted to β,β' -disulfopropionic acid. Reacting with ammonium bisulfite, α -bromo and β -chlorocrotonic acids yield the same β -sulfo crotonic acid, and a disulfobutyric acid, possibly the β,β -compound.¹⁵⁴

The carbonyl group in benzoylacrylic acid exerts an activating influence and this compound reacts instantly in the cold with sodium bisulfite.¹⁵⁵

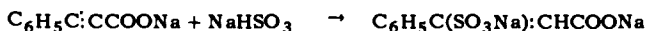
The reaction between coumarin and sodium bisulfite apparently proceeds in the following manner:¹⁵⁶



If an alkyl or aryl group is attached to either of the unsaturated carbon atoms, no addition takes place; an acetyl or a carbethoxy group does not exert such an inhibitive action. 3,6-Dinitrocoumarin reacts with sodium bisulfite to form 5-nitrosalicylaldehyde.

Sodium bisulfite does not react with umbelliferone, daphnetine, diethylesculetin and triethylesculetinic acid.¹⁵⁷

Acetylenic acids and their esters add bisulfites, propiolic acid giving ammonium *trans*- β -sulfoacrylic acid with ammonium bisulfite.¹⁵³ *Sym*-*dl*-disulfosuccinic acid is obtained from acetylenedicarboxylic acid and alkali bisulfites; the same compound may also be obtained from bromomaleic or bromofumaric acid and a bisulfite. Methyl phenylpropiolate and methyl *n*-amylpropiolate both give mono and disulfonates with sodium bisulfite, whereas sodium phenylpropiolate adds only one mole of the reagent:



As in olefinic acids, the unsaturated bond in olefinic aldehydes and ketones is activated and is capable of adding bisulfites.¹⁵⁸ Since the carbonyl group in aldehydes and in many ketones¹⁵⁹ also reacts with bisulfites additively, the end product of the reaction is often the sulfonate of the bisulfite addition product of the carbonyl compound. The aldehyde group in general reacts more readily with bisulfite than the olefinic bond.

Citral reacting in the cold with sodium bisulfite in the presence of a very slight excess of sulfurous acid gives the normal aldehyde bisulfite addition product,



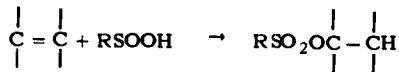
which separates in fine, sparingly soluble plates. Regeneration of citral from this addition product is not, however, quantitative. When the aldehydebisulfite compound is allowed to stand, or is gently warmed with an excess of bisulfite, it goes into solution as a labile dihydrodisulfonic derivative from which citral may be regenerated by the action of sodium hydroxide but not by use of alkali carbonates. If the solution of the labile dihydrodisulfonic derivative is strongly heated a stable dihydrodisulfonic derivative is formed which can no longer be converted to citral. Citral is capable also of forming a labile and stable trihydrosulfonate. In acetic acid solution, only the normal aldehyde bisulfite addition compound is formed.

The reaction of sodium bisulfite at 0°, in the absence of any excess of sulfurous acid, with citronellal, in which the double bond is not conjugated with the carbonyl group, results in the formation of the normal aldehyde bisulfite compound; but addition at the double bond also takes place in the presence of some sodium sulfite.

Pulegone gives the normal addition product with sodium bisulfite, but a sulfonic acid also results when the compound is treated at 20° with an alcoholic solution of sulfur dioxide.¹⁶⁰

Reaction with Sulfonic Acids

Olefins with few exceptions react with sulfonic acids to form sulfonic esters:¹⁶¹



Ethylene and acetylene fail to react in this manner with sulfonic acids.

The point of attachment of the sulfonic group is determined by Markownikow's rule.

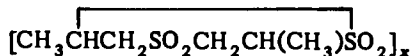
Sulfonic esters are stable only when in the pure condition and free of any acids. As obtained by the reaction of sulfonic acids with unsaturated compounds, they are reasonably stable, some decomposing at temperatures slightly in excess of 0°, others remaining unchanged at 60°. When freed from unreacted acid, they may be distilled under reduced pressure without decomposition. These esters polymerize readily when subjected to excessive temperatures.

Methanesulfonic esters have been prepared in yields ranging 60-80% from propylene,

in 100% yield from 2-butylene and in 90% yield from 1-pentene, using purified methane sulfonic acid in the reaction.

Reaction with Sulfur Dioxide

Many olefins react with sulfur dioxide in the presence of certain catalysts, such as peracetic acid and ascaridole, especially readily in acid solution, to form amorphous white compounds containing sulfur.¹⁶² The compound obtained from propylene has been assigned the structure



This polymer has a molecular weight in excess of 50,000. The polymers obtained from vinyl chloride and vinyl bromide differ from those of many other unsaturated compounds in that two molecules of the halide are combined with one of sulfur dioxide. The structure of the chloro compound is represented as



Mixed polymers have also been obtained containing two different hydrocarbon groups.¹⁶⁴ The mixed polymer from 1-pentene and undecylenic acid appears to have a well-defined structure.

In many instances reaction proceeds only at a low temperature. Reaction takes place at 4° with isobutylene in the presence of lithium nitrate, but not at room temperature.⁴⁷⁵ Trimethylethylene, tetramethylethylene, pinene and dihydronaphthalene fail to react with sulfur dioxide. Allyl and cinnamyl bromides fail to react and inhibit the reaction of other olefins with sulfur dioxide, even when present in small amounts. Phenyl and alkyl acetylenes form polymers with sulfur dioxide, but dialkyl acetylenes and allene do not react.¹⁶⁵ Polymers obtained from alkyl acetylenes are less stable than those derived from olefins, and release half the amount of SO₂ they contain when they are heated to 100-140°. ¹⁶⁶

Dienes reacting with sulfur dioxide in the presence of stabilizing agents such as polyhydric phenols yield cyclic sulfones. Butadiene forms the unsaturated sulfone

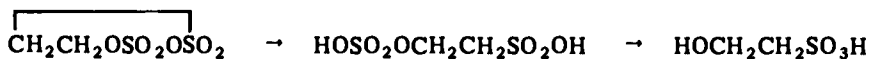
$\overbrace{\text{CH}_2\text{CH}=\text{CHCH}_2\text{SO}_2}$, and substituted butadienes behave similarly.⁴⁷⁶ Such unsaturated sulfones have been converted by hydrogenation to saturated bodies termed sulfolanes.⁴⁷⁷

Sulfonic acid derivatives of sabinene, sabinol and pulegone are formed when sulfur dioxide is passed into the alcoholic solution of these unsaturated compounds.¹⁶⁷ Sulfonic acid derivatives have been obtained most frequently from compounds in which a carbonyl group is adjacent to the ethylenic bond,¹⁶⁸ that is, containing the group $-\text{CH}=\text{CH}.\text{CO}$.

Reaction with Sulfur Trioxide

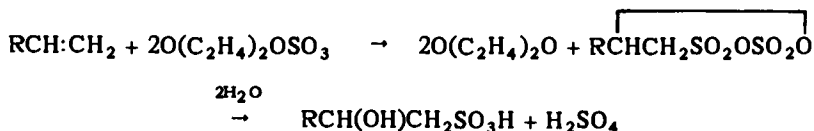
Unsaturated compounds react energetically with sulfur trioxide and, under ordinary experimental conditions, the hydrocarbon is generally oxidized. A

definite compound, the crystalline carbyl sulfate, $\overbrace{\text{CH}_2\text{CH}_2\text{OSO}_2\text{OSO}_2}$, may be obtained easily from ethylene. This yields, on stepwise hydrolysis, first ethionic acid, then isethionic acid:

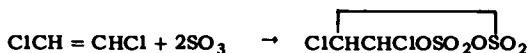


The reaction with the higher homologs of ethylene is complex.

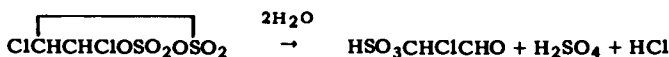
Olefins with a terminal double bond react with the dioxane-sulfur trioxide complex to give the higher homologs of carbyl sulfate anhydride, which may be readily hydrolyzed to the corresponding hydroxy sulfonic acids:⁴⁷⁸



The reaction of sym-dichloroethylene with fuming sulfuric acid results in the formation of the dichloro derivative of carbyl sulfate anhydride:

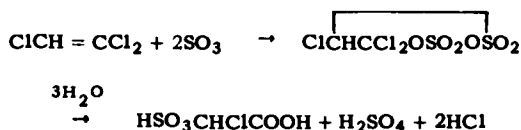


Hydrolysis with 60% sulfuric acid leads to the formation of *sulfochloracetaldehyde*:¹⁶⁹



β -Sulfopropionaldehyde, -butyraldehyde, and - α -methylvaleraldehyde have been prepared by this method from the appropriate halogenated unsaturated compounds.¹⁷⁰

Treatment of trichloroethylene with fuming sulfuric acid, followed by hydrolysis, similarly leads to the formation of *sulfochloracetic acid*:¹⁷¹



Hydroxy sulfonic acids result from olefins under the combined action of sulfur dioxide and chlorine. This reaction has been discussed in the section dealing with sulfonic acids, under the heading *Reed's reaction*.

Reaction of Olefins with Hydrogen Sulfide and Mercaptans

Hydrogen sulfide reacts with few unsaturated compounds under ordinary conditions, notably with certain unsaturated ketones and nitro olefins.¹⁷² Combination with hydrocarbons has been brought about, however, under high pressure at elevated temperatures, usually not exceeding 200°. The reaction is catalyzed by elemental sulfur. The mercaptans and sulfides obtained are all *normal* addition products, combination taking place in accordance with Markownikow's rule.¹⁷³ By far the most effective catalyst is reported to be a silica-alumina combination containing 1 to 5% alumina.⁴⁷⁹ The effective temperature range is 93 to 150°. The method has been employed commercially for the synthesis of a large number of mercaptans, particularly those

with 12 carbon atoms. Hydrofluoric acid, boron trifluoride, $\text{BF}_3 \cdot \text{H}_2\text{O}$, and borontrifluoride phosphoric acid, $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$, are also effective catalysts, and bring about the combination of hydrogen sulfide with diisobutene and triisobutene at ordinary temperature.⁴⁸⁰ Sulfuric acid is also known to bring about the addition of hydrogen sulfide to certain olefins at ordinary temperature.⁴⁸¹

Isoprene reacts with hydrogen sulfide in the presence of ferric oxide at 96° to form mercaptans, probably of the structure $(\text{CH}_3)_2\text{C}(\text{SH})\text{CH}=\text{CH}_2$ and



Terpenes react very readily with hydrogen sulfide forming mercaptans.⁴⁸³

Mercaptans react with some unsaturated hydrocarbons and unsaturated ketones and acids. The reaction is accelerated by strong acids and bases.¹⁷⁴ No significant reaction takes place with ethylene and propylene at ordinary temperature, but combination takes place, for example, with ethyl mercaptan and trimethylene mercaptan when these compounds are heated with the olefins under pressure in the presence of sulfur. Addition generally takes place, contrary to Markownikow's rule, in the absence of catalysts favoring the normal addition, a fact which led Posner to formulate the rule that the sulfur atom in the mercaptans attaches itself to the carbon atom bearing the greater number of hydrogen atoms. As usual, the abnormal addition is accelerated by oxygen and light, and is inhibited by hydroquinone and piperidine.¹⁷⁵ Elemental sulfur and sulfuric acid catalyze the normal addition. In reactions with unsaturated compounds in which the olefinic bond is conjugated with a carbonyl group, the sulfur atom invariably becomes attached to the β -carbon atom.¹⁷⁶ Such compounds react quite readily with mercaptans at 100° .

*Thiophenol*¹⁷⁷ and *benzyl mercaptan* react with a large number of unsaturated compounds, though they fail to combine with stilbene and 1,4-diphenylbutadiene.

Mercaptoacetic acid, cysteine and glutathione combine with maleic acid, but fail to react with fumaric, citraconic, mesaconic, and α -phenyl- β -styryl maleic acids; they fail to react also with *cis* and *trans* cinnamic acids. Mercaptoacetic acid reacts with styrene and isobutylene in the presence of peroxides, forming the compounds



and $(\text{CH}_3)_2\text{CHCH}_2\text{SCH}_2\text{COOH}$ respectively.¹⁷⁸ No addition occurs in the presence of quinol.

Mercaptans react with nitro olefins in the presence of a basic catalyst to form nitroalkyl thio ethers.

Reaction with Sulfur Monochloride

Sulfur monochloride reacts with certain unsaturated compounds to form chloro monosulfides:⁴⁸⁴



Reaction proceeds in this manner with ethylene, propylene, β -butylene and styrene. A chloro disulfide is obtained with compounds such as trimethylene,

β -methyl- Δ^{β} -butylene and allyl chloride which react at a lower temperature, these olefins also yield a sulfide if the reaction is carried out at a higher temperature.

Sulfuryl chloride, SO_2Cl_2 , acts as a chlorinating agent toward olefins, and seems very well suited for the purpose of preparing dichloro addition products from unsaturated compounds. Tetraphenylethylene dichloride, $(\text{C}_6\text{H}_5)_2\text{CClCl}(\text{C}_6\text{H}_5)_2$, may be obtained, for example, from tetraphenylethylene.¹⁷⁹

Aryl sulfenyl chlorides add to ethylene to give β -chloroethyl aryl sulfides in 60 to 80% yield:⁴⁸⁵



Certain other olefinic bodies react similarly. Vicinal halogen atoms in olefins decrease the reactivity of the double bond, and 1,2-dichloroethylene fails to react. No reaction takes place with an olefinic bond that is conjugated with a carbonyl, carboxyl, or a cyano group. In the reaction with isobutylene, the chlorine attaches itself to the carbon atom with the fewest hydrogen atoms. *p*-Nitrophenyl- and *p*-chloro-*o*-nitrophenylsulfenyl halides generally react vigorously with ordinary olefins. The former reacts with stilbene while the latter fails to react with this compound.⁴⁸⁶

Aryl sulfenyl thiocyanates, RSSCN , react with unsaturated compounds in the manner of aryl sulfenyl chlorides.⁴⁸⁷

Reaction with Phosphorus Chlorides

Phosphorus pentachloride reacts with unsymmetrical olefins of the type



in the cold to form addition compounds $\text{RR}'\text{CClCH}_2\text{PCl}_4$. When these products are treated with water, they are converted to unsaturated phosphonic acids $\text{RR}'\text{C} = \text{CH}_2\text{PO}(\text{OH})_2$. Reaction with alkylenes, $\text{RCH} = \text{CH}_2$, leads to the formation of $\text{RCHPCl}_4\text{CH}_2\text{Cl}$,¹⁸⁰ although styrene gives the normal addition product $\text{C}_6\text{H}_5\text{CHClCH}_2\text{PCl}_4$, which is hydrolyzed to styrenephosphonic acid,

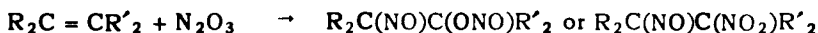


The reaction is applicable to aryl substituted acetylenes $\text{RC} \equiv \text{CH}$, the addition product $\text{RCCl} = \text{CHPCl}_4$ giving $\text{RCCl} = \text{CHPO}(\text{OH})_2$ on treatment with water.¹⁸¹

Phosphorus trichloride gives addition products with α,β -unsaturated ketones; treated with water, these products are converted to saturated phosphonic acids.³⁹¹

Reaction of Olefins with Nitrogen Oxides and other Nitrogen Compounds

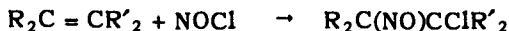
Many alkylenes, and especially the higher members of this series, react with nitrogen trioxide, nitrogen tetroxide¹⁸² and nitrosyl chloride,¹⁸³ forming adducts of a greenish blue color. Nitrogen trioxide gives principally nitrosites or pseudonitrosites:⁴⁸⁸



Nitrosates and dinitro compounds are obtained with nitrogen tetroxide:



while nitrosyl chloride gives nitroso chlorides:



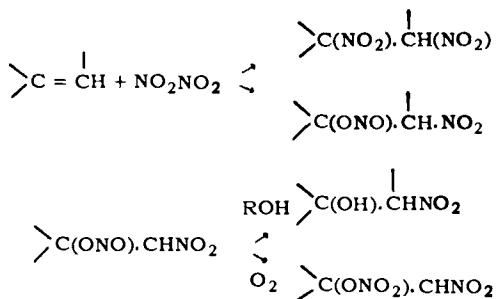
The reaction is generally applicable to unsaturated compounds of all descriptions. The resulting compounds readily polymerize¹⁸⁴ to colorless, crystalline dimeric forms, such as $[(CH_3)_2C(ONO)CHCH_3]_2N_2O_2$; they revert to the monomeric form, however, when fused or when in solution.¹⁸⁵

Nitrogen pentoxide converts trimethylethylene to amylene nitrosate, but reacts with tetramethylethylene¹⁸⁶ to form a mixture of the compounds $(CH_3)_2C(NO)C(ONO_2)(CH_3)_2$, $(CH_3)_2C(NO_2)C(ONO_2)(CH_3)_2$ and $(CH_3)_2C(ONO_2)C(ONO_2)(CH_3)_2$.

The reaction of *nitrogen tetroxide* with unsymmetrical olefins, leads to the formation of nitro nitrites. The nitro group invariably attaches itself to the carbon atom bearing the greater number of hydrogen atoms.

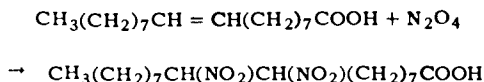
The solvent exerts an important effect on the direction in which the reaction proceeds. Hydrocarbons and chlorinated hydrocarbons favor the formation of the nitrate ester, while *sym* ethers, dioxane and methylal favor the normal addition.

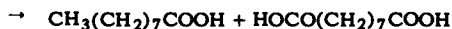
The reaction with nitrogen tetroxide¹⁸⁷ is carried out at -10 to 25° . The gaseous olefins are absorbed or dissolved in the liquid tetroxide or in a solution of the same, with cooling. Ethylene reacts slowly, while other olefins react more rapidly. After completion of the reaction, the excess tetroxide and the solvent are removed by evaporation under vacuum, preferably from a falling warm film. When the latter method is used, the residue may be run directly into water or methanol. The final product obtained then consists of the dinitro compound, a nitro alcohol, and a nitro nitrate:



It should be noted that nitronitrites $>C(ONO).CHNO_2$ are highly unstable, explosive compounds.

Olefinic acids readily add nitrogen tetroxide to form dinitro carboxylic acids which, when heated with concentrated hydrochloric acid, yield mono and dicarboxylic acids:¹⁸⁸





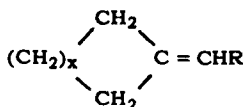
The reaction may therefore serve for the location of the position of the double bond in unsaturated acids.

Tetramethylethylene gives tetramethylethylene dinitrite, $(\text{CH}_3)_2\text{C}(\text{ONO})\text{C}(\text{ONO})(\text{CH}_3)_2$, both with nitrogen trioxide and nitrogen tetroxide, together with a small amount of *sym*-dinitrotetramethylethane.

The formation of nitroso halides from nitrosyl halides and olefins depends upon the structure of the latter. Reaction takes place with olefins of higher molecular weight in which at least one alkyl group is attached to each of the unsaturated carbon atoms.¹⁸⁹ Olefins in which neither carbon atom bears a hydrogen atom cannot be converted to isomeric or polymeric forms. The reaction has been of great value in the field of terpenes.⁴⁸⁸

The procedure employed for the preparation of nitroso halides is to conduct gaseous nitrosyl chloride into a well-cooled solution of the olefin in two or three volumes of chloroform, the nitroso chloride being precipitated by the addition of methanol to the solution upon completion of the reaction. A convenient alternative method is to add concentrated hydrochloric acid carefully to a well-cooled solution of amyl or ethyl nitrite and the olefin in alcohol or in acetic acid.

Nitroso chlorides have been obtained from trimethylethylene, tetramethylethylene, cyclohexene, methane derivatives of the type $\text{R}_2\text{C} = \text{CH}_2$, and from hydrocarbons having a semicyclic double bond and a side chain, such as



Ethylene gives ethylene dichloride, while propylene gives a dichloride and a nitroso chloride.

The nitroso chloride derived from trimethylethylene changes to the isomeric methyl chloroisopropyl ketoxime on long heating at 75° ; the colored monomer changes to the dimer, bis-trimethylethylenenitrosochloride, $[(\text{CH}_3)_2\text{CClCH}(\text{CH}_3)_2]_2\text{N}_2\text{O}_3$.

Nitroso chlorides may be converted to oximes from which ketones may be obtained by hydrolysis. This offers a method for the identification of unsaturated compounds.

Addition reactions are observed also with nitrogen trichloride,¹⁹⁰ and with hydrazoic acid.

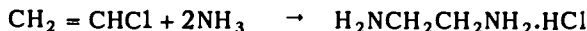
Nitrogen trichloride adds on to 2-butene to form 2-chloro-3-(dichloroamino)-butane, $\text{CH}_3\text{CHClCH}(\text{NCl}_2)\text{CH}_3$, which is converted by concentrated hydrochloric acid to 2-chloro-3-aminobutane. 1-Butene gives 1-chloro-2-(dichloroamino)-butane. Trimethylethylene reacts rapidly with nitrogen trichloride, the reaction products being amylene chlorides, nitrogen and ammonium chloride. The addition of nitrogen trichloride to olefins apparently proceeds in accordance with Markownikow's rule, if the assumption is made that the mobile chlorine atom in nitrogen trichloride is electropositive.

N-Alkyl- β -bromo- β -phenethylsulfonamides have been prepared through the reaction of N-alkyl-N-bromosulfonamides with styrene:⁴⁰⁵

Reaction takes place readily when the unsaturated bonds are in the close proximity of carbonyl, carboxyl and other activating groups, the amino group entering the β -position.¹⁹⁴ Combination takes place on warming a mixture of the unsaturated compound and ammonia or amines in a sealed tube at 100-105°. Unsaturated acids with two double bonds are capable of adding two molecules of amine.¹⁹⁵ Methylamine reacting with ethyl crotonate replaces the ethoxy group and also adds at the double bond.¹⁹⁶ α,β -Unsaturated ketones combine with ammonia and amines very readily,¹⁹⁷ the amino group joining to the carbon atom further removed from the carbonyl group. Thus, mesityl oxide reacting with ammonia gives diacetoneamine, $\text{CH}_3\text{COCH}_2\text{C}(\text{NH}_2)(\text{CH}_3)_2$.¹⁹⁸

Unsaturated nitriles, such as acrylonitrile, $\text{CH}_2 = \text{CHCN}$, readily add ammonia and simple aliphatic amines to form β -aminobutyronitrile and its derivatives.¹⁹⁹ Higher aliphatic amines, such as diethylamine, isobutylamine and ethylene diamine do not add to vinylacetoneitrile, $\text{CH}_2 = \text{CHCH}_2\text{CN}$, but cause its isomerization to a mixture of crotonic nitriles. Aromatic amines also fail to add to this nitrile, although aniline reacts at its boiling point in the presence of cuprous chloride or cupric oxide with the evolution of considerable ammonia.²⁰⁰

Ethylene derivatives which contain a halogen attached to one of the unsaturated carbon atoms, such as vinyl chloride, react with ammonia with replacement of the halogen and addition at the double bond:²⁰¹



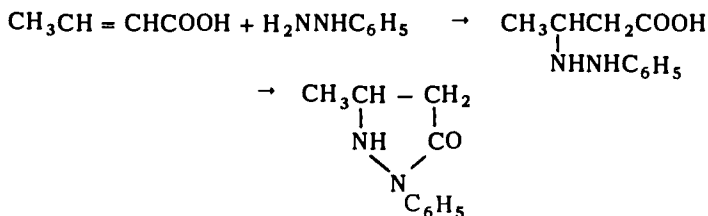
Aryl amines add at the double bond of bromonitrostyrene.²⁰²

Nitro olefins also react additively with primary and secondary aliphatic as well as aromatic amines to form 2-nitro alkyl amines.

Olefins such as trimethylethylene, butadiene, cyclohexene and 1,4-dihydronaphthalene add certain aryl amines, although the reaction does not proceed simply, and carbon to carbon unions as well as carbon to nitrogen unions occur.²⁰³

Hydroxylamine also adds at the multiple bond of unsaturated acids; the hydroxylamino acid first formed is reduced on longer heating with excess of hydroxylamine, and an amino acid results.²⁰⁴ The hydroxylamino group enters the β -position with respect to the carboxyl group, atropic acid forming an exception and giving α -oxamino- α -phenylpropionic acid.²⁰⁵ Hydroxylamine also adds at the double bond of unsaturated ketones of the aliphatic and aromatic series to form hydroxylamino ketones.²⁰⁶ Allyl ketones $\text{CH}_2 = \text{CHCH}_2\text{COR}$ react normally to give oximes, as do also propenyl and vinyl ketones.²⁰⁷

Phenyl hydrazine reacts with α,β -unsaturated acids to form pyrazolidones:²⁰⁸



*Urea*²⁰⁹ and *semicarbazide*²¹⁰ also are known to react additively with unsaturated carbonyl compounds.

Addition of Hydroxy Compounds to Olefins

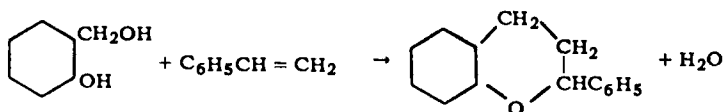
Addition of alcohols to ethylenic double bonds can occur in the presence of metallic sodium. Addition would appear to take place with, among others, olefins in which a halogen atom is attached to one of the unsaturated carbon atoms: thus, α -bromobenzalacetophenone is capable of adding methanol, ethanol, normal and isopropyl alcohols and butanols in the cold, in the presence of a little sodium alcoholate:



The addition products lose the elements of hydrogen bromide when heated in an alkaline medium, giving enol ethers, $\text{C}_6\text{H}_5\text{COCH} = \text{C(OR)C}_6\text{H}_5$. ω -Nitrostyrene, $\text{C}_6\text{H}_5\text{CH} = \text{CHNO}_2$, and α -nitrocinnamic esters also add alcohols readily.

The addition of alcohols to olefinic compounds is catalyzed by sulfuric acid and by aluminum chloride.²¹¹ Methoxyphenylethane, $\text{C}_6\text{H}_5\text{CH(OCH}_3\text{)CH}_3$, has been obtained, for example, in 90% yield through the reaction of methanol with styrene at 135-150° in the presence of sulfuric acid.²¹²

The reaction of styrene with saligenin at boiling temperature gives a cyclic product in 57% yield:²¹³



The double bond in tetrafluoroethylene and trifluorochloroethylene adds alcohols in the presence of a basic catalyst to form ethers. Direct addition of alcohols has been observed with other olefins.⁴⁰⁶

Phenols have been condensed in the cold with unsaturated compounds under the influence of mineral acids or boron trifluoride to phenolic ethers. Alkylated phenols are formed if the reaction is carried out at high temperatures.⁴⁸⁹

Vinyl ethers result through the reaction of alcohols with *acetylene*. The reaction proceeds at high temperatures without the use of a catalyst. The addition of alcohols to acetylenic ketones takes place readily in alkaline media. The method makes possible the preparation of isomeric ethers $\text{R}'\text{COCH}:\text{C(OR)R}''$ and $\text{R}'\text{C(OR)} = \text{CHCOR}''$ of the enols of 1,3-diketones $\text{R}'\text{COCH}_2\text{COR}''$.

Vinyl ethers warmed slightly with dilute acids are hydrolyzed instantaneously to acetaldehyde and alcohol. The reaction takes place with water alone at 100°.

Olefins of the type $\text{R}_2\text{C} = \text{CH}_2$ react additively with formaldehyde, addition taking place at the dual bond between oxygen and carbon in the aldehyde, and resulting in the formation of substituted allyl alcohols, $\text{R}_2\text{C} = \text{CHCH}_2\text{OH}$.⁴⁰⁷ Reaction with N-methylformanilide results in the formation of an aldehyde



with elimination of methyl aniline.⁴⁰⁸ Such olefins are also capable of coupling with diazonium compounds forming azo dyes of the type $R_2C = CHN = NAr$.⁴⁰⁹

Reaction of Organic Acids with Olefins; Reaction with Carbon Monoxide

Alkylenes may be transformed to alkyl esters by reaction with organic acids such as formic, acetic, propionic or butyric acids. Acetic acid, for example, reacting with trimethylethylene, gives the acetic ester of *tert*-amyl alcohol:

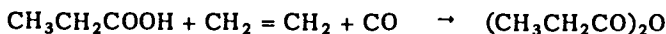


This reaction takes place very slowly even at high temperatures.²¹⁴ The reaction is catalyzed by zinc chloride. Chloracetic acids react much more readily than acetic acid.²¹⁵ Acid chlorides²¹⁶ and anhydrides also react additively with alkylenes in the presence of zinc chloride.

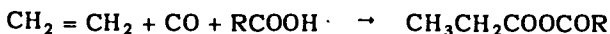
Olefins, including those of the type $R_1CH = CHR_2$ and cycloolefins of the type cyclohexene, may be made to react with *carbon monoxide* and water at temperatures in the neighborhood of 300° and under 700 atmospheres pressure in the presence of acid catalysts and certain solids offering a large contact surface, to yield saturated acids.⁴¹⁰ Reaction takes place under more moderate conditions, viz., in the temperature range 200-300° and under 150-300 atm pressure when nickel carbonyl is used as a catalyst:



Reaction with ethylene results in the formation of as much as 50% propionic anhydride:

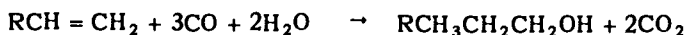


Reaction with alcohols and phenols results in the formation of esters; reaction with mercaptans gives thio esters, while reaction with acids yields anhydrides:

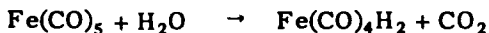


The reaction is applicable to alicyclic olefins. Cyclohexanoic acid is formed, for example, when cyclohexene is heated with carbon monoxide and water in the presence of nickel carbonyl.

The reaction of olefins with carbon monoxide and water may result in the formation of an alcohol when iron hydrocarbonyl is employed as a catalyst:



The reaction may be explained by assuming that iron hydrocarbonyl reacts with carbon monoxide to form iron pentacarbonyl and hydrogen, the latter reacting with the olefin in conjunction with carbon monoxide to form the alcohol. The iron pentacarbonyl reacts with water in the presence of an alkaline agent to regenerate the iron hydrocarbonyl:

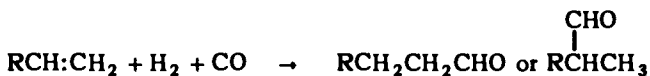


The reaction may be carried out with nickel carbonyl alone, this compound serving as the source of carbon monoxide.

Isovaleric acid may be obtained, for example, from a mixture of 1-butene, nickel carbonyl and acetic acid sufficient to combine with the liberated nickel by heating several hours at 160-170°. The ethyl ester of the acid is obtained in quantitative yield when water in the mixture is replaced with ethanol, and the mixture is heated for 24 hours. The reaction with octene and ethyl alcohol proceeds well at 200°. Side reactions are reduced to a minimum by carrying out the reaction as rapidly as possible. The unconverted portions of the olefin may, generally, be recovered to a large extent and recycled in the process.

The Oxo Reaction⁴⁹⁰

The simultaneous reaction of carbon monoxide and hydrogen with olefins takes place under pressure and at elevated temperatures in the presence of certain catalysts. The primary product of the reaction is an aldehyde with one carbon atom more than the olefin:



This reaction, which was discovered by Roelen, is termed the Oxo reaction. The process is one of hydroformylation.

Finely divided cobalt and salts of this metal are excellent catalysts for the reaction.⁵²⁸ The original Fischer-Tropsch catalyst consisting of 30% cobalt, 2% thorium oxide, 2% magnesium oxide and 66% diatomaceous earth, has given satisfactory results. Compounds of cobalt such as the acetate, carbonate or oxide may be employed with good results in the temperature range 150 to 160°. Sulfur compounds do not cause poisoning of the catalyst.

The reaction proceeds at a satisfactory rate at temperatures varying between 100 and 200°, depending on the type of olefin. Low molecular weight olefins react at lower temperatures than those of high molecular weight. The optimum temperature depends on the activity of the catalyst as much as on the character of the olefin. Dicobalt tetracarbonyl, $\text{Co}_2(\text{CO})_8$, appears to be the actual catalyst.⁴⁹² This is borne out by the fact that reaction proceeds at a satisfactory rate at a temperature at which dicobalt carbonyl would form at an appreciable rate under the conditions of the reaction.

The aldehyde is the principal product of the reaction at temperatures up to 180°. Above this temperature the aldehyde is reduced to the corresponding alcohol. If the aldehyde is the desired product, the reaction is carried out at the lowest possible temperature and under a high pressure. Used catalysts give better yields of aldehyde; sulfur compounds also favor the formation of aldehyde in preference to the alcohol. In preparing sensitive aldehydes it is desirable to use the preformed cobalt carbonyl. If alcohols are desired as the final product, the reaction is carried out in the temperature range 180 to 200°. ⁴⁹¹

Benzene, toluene, alcohols, ether, acetic anhydride have been used as sol-

vents in the Oxo reaction.⁵²⁶ Best yields of aldehydes are obtained when the reaction is carried out in the presence of orthoformic ester.⁵²⁷ The latter rapidly acetylates the aldehyde formed and thus prevents side reactions.

The Oxo reaction is strongly exothermic. The molecular heat of formation of gaseous propionaldehyde from propylene, for example, is 34.75 Cal.⁵²⁸

The Oxo reaction may be carried out in the laboratory by use of solutions of cobalt carbonyl as a catalyst, or of solutions of other cobalt compounds.⁵²⁹ Stainless steel autoclaves may be employed providing the reaction period is short, otherwise autoclaves or other equipment constructed of special carbon monoxide-resistant steels should be used.⁵³⁰ Cobalt carbonyl is an extremely poisonous volatile compound and should be handled with due precautions.

When the reaction is carried out in aqueous medium, a solution of 350 gm cobalt sulfate heptahydrate per liter is used the pH of which is adjusted to 2.5 with nitric acid. The addition of iron to the catalyst solution is considered to be of advantage. As a rule, 10 to 20% by volume of catalyst solution is added to the olefin. The reaction is carried out under 200 atm pressure and at temperatures ranging 130 to 160°. In general there is an appreciable induction period when the reaction is carried out with an aqueous catalyst. The reaction proceeds at a satisfactory rate under 10 to 20 atm pressure with liquid olefins providing the gases and liquid are brought into intimate contact.⁵³¹

The course of aldehyde formation may be followed by adding excess 4% hydroxylamine hydrochloride to samples of known weight or volume of the reaction mixture and titrating the liberated hydrochloric acid.⁵³² A more satisfactory procedure is to add excess phenylhydrazine hydrochloride to the sample, to oxidize the unreacted phenylhydrazine with Fehlings solution and to determine the evolved nitrogen.⁵³³

When carrying out the Oxo reaction on the industrial scale, towers packed with granular catalyst have been employed. The catalyst is heated in these by tubes through which hot water under pressure is circulated. The reaction may also be carried out in the liquid phase with the higher olefins, using finely divided catalyst dispersed in the liquid. Catalyst activity decreases through gradual loss of cobalt due to the formation of the volatile cobalt carbonyl, a portion of which is carried away by the circulating gases. Catalyst activity is maintained by the continual introduction of the cobalt salt of a higher fatty acid or a naphthenic acid into the reaction mixture with the olefin feed.

After the conclusion of the reaction any catalyst in suspension in the reaction mixture may be filtered and the product recovered by distillation. A considerable quantity of the catalyst goes in solution into the reaction mixture. Removal of the dissolved catalyst may be effected by the addition of 5% sulfuric acid, potassium bisulfate or with water and carbon dioxide under pressure at 40°. ⁵³⁴ Another procedure is to mix the reaction product with an aqueous iodine-potassium iodide solution, or a solution of iodine in pyridine. All cobalt carbonyl compounds react with iodine with complete destruction of the carbonyl and formation of carbon monoxide and cobalt iodide. The cobalt in solution may also be precipitated, quantitatively as metallic cobalt, by heating the reaction mixture at 100 to 135° for 45 minutes under 1000 to 1500 lb hydrogen pressure.

Numerous *by-products* may form in the course of the Oxo reaction. An aldol condensation may occur, especially in the presence of finely divided metals. Partial polymerization of the lower olefins takes place; the olefin and the aldehyde formed in the reaction may be reduced; Cannizzaro's reaction may take place and acetals may form. Sometimes *sym*-diketones are formed through the condensation of the aldehyde with a molecule of the olefin. When the Oxo reaction proceeds slowly in the presence of cobalt hydrocarbonyl, migration of the double bond in the olefin may take place.⁵³⁵

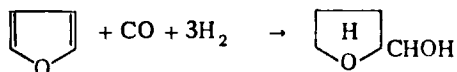
Finely divided metallic cobalt is prepared by the reduction of cobalt oxide with hydrogen. The reduction is carried out at the lowest possible temperature, generally between 350 and 450°, and as rapidly as possible. It is best not to carry the reduction to the point where all the oxide has been reduced, but to stop the operation when 60 to 70% of the oxide has been reduced. Oxides and hydroxides of alkali metals act as activators of the catalyst. Chromium, manganese, thorium and magnesium have also been claimed to have an activating influence.⁵³⁴ Iodine acts as an activator by virtue of the fact that it facilitates the formation of cobalt carbonyl.

Dicobalt octacarbonyl is prepared in the following manner: A mixture of 30 gm cobalt carbonate and 100 cc benzene is placed in a 500 cc "Aminco" stainless steel autoclave; a pressure of 3,200 lb is established with a 1:1 "synthesis" gas and the autoclave is heated at 180° for two hours. After cooling the liquid, which contains about 0.25 gm dicobalt carbonyl per cc, is filtered by centrifuging. It should be stored in the cold, preferably under one atmosphere carbon monoxide pressure.

If pure crystalline dicobalt octacarbonyl is the desired product, the solution is evaporated under vacuum, never allowing the temperature to exceed 30°. The last traces of benzene are removed by pressing the solid between pieces of filter paper, an operation which should be performed as rapidly as possible and should not be carried out with quantities in excess of 20 grams. The crystalline compound is kept in the cold under an atmosphere of carbon monoxide.

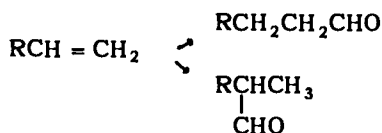
The *Flischer-Tropach catalyst* is prepared as follows: A solution of 310 gm cobalt nitrate in 2.5 liters water and one of 11 gm of thorium nitrate in 2.5 liters water are mixed and heated to boiling, then 12 gm magnesium oxide and 200 gm diatomaceous earth are introduced with agitation, and 183 gm of anhydrous sodium carbonate in 2 liters water are added. Boiling is continued for two hours with the mass kept well stirred. The solid is finally filtered, washed free of any soluble salt with hot distilled water, and is dried at 110°. The dried mass is reduced in a flask or a tube. This operation is carried out by heating the mass at 390 to 405° and passing a stream of hydrogen over it at the rate of 500 to 600 liters per hour per 100 cc (26.6 gm) of catalyst mass for two hours. The reduced catalyst is cooled in a stream of hydrogen, and is kept under a carbon dioxide atmosphere, if it is not to be used immediately.

A great variety of olefinic hydrocarbons have been subjected to the Oxo reaction and all have been found to react quantitatively. A large number of olefinic bodies with functional groups have also been subjected to the reaction and with very few exceptions, have been found to react satisfactorily. The olefinic bond in α,β -unsaturated aldehydes and ketones is reduced under the conditions of the Oxo reaction. Olefins in which a halogen is attached to one of the unsaturated carbon atoms fail to react.⁵³⁰ In *conjugated dienes*, one olefinic bond is reduced while the other is hydroformylated. Thus, 1,3-butadiene gives *n*-valeraldehyde, and 2,3-dimethylbutadiene-1,3 yields 3,4-dimethylpentanal. The Oxo reaction fails to proceed with *aromatic compounds*. Furan subjected to the reaction at 160 to 180° gives tetrahydrofurfuryl alcohol:



2,5-Dimethyl furan similarly gives 2,5-dimethyl-3-tetrahydrofurfuryl alcohol. Thiophene fails to undergo the hydroformylation reaction, but is slowly hydrogenated to thiolane.

Straight chain olefins with the double bond at the end of the chain, subjected to the Oxo reaction, yield two isomeric aldehydes in almost equal quantities:

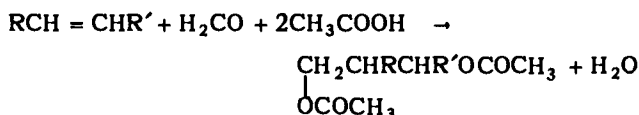


Straight chain olefins with the double bond at positions other than the end of the chain, subjected to the Oxo reaction, give products which are almost identical with those obtained from the isomeric straight chain olefins with the unsaturation at the end of the chain.⁵³⁶

Olefins possessing the structure $\text{RC}(\text{CH}_3) = \text{CH}_2$, when subjected to the reaction, give exclusively the aldehydes $\text{RCH}(\text{CH}_3)\text{CH}_2\text{CHO}$. When a branched chain olefin is hydroformylated, the products are almost identical with those obtained from the isomeric olefins with the double bond at the terminal position.

Addition of Formaldehyde to Olefins; Prins Reaction

Formaldehyde reacts with unsaturated compounds in the presence of acetic acid and sulfuric acid to form the diacetate of a glycol:⁴⁹⁴

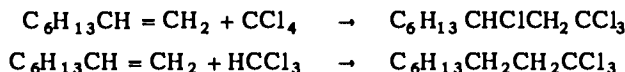


A formal or a dioxane, $\text{RCC}(\text{R}')\text{CH}_2\text{OCH}_2\text{O}$, is formed simultaneously.

Since Prins' reaction makes possible the preparation of a large variety of 1,3-glycols, and since these may be readily converted to the corresponding 1,3-halides, it is possible to obtain a great number of conjugated dienes by use of this reaction.

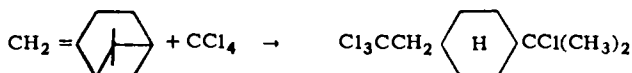
Addition of Halogenated Compounds to Olefins

Carbon tetrachloride and chloroform react with olefins when heated in the presence of small amounts of diacetyl- or dibenzoyl peroxide, 0.02 molal concentrations of these compounds being effective.²¹⁷ Thus, octane-1 gives a tetrachloro and a trichlorononane with these chlorinated hydrocarbons:



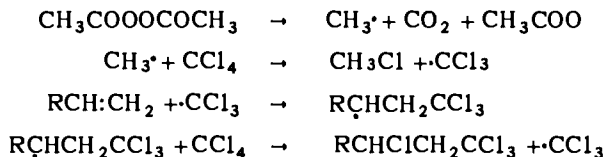
The yields in many cases exceed 60% of the theoretical.

Carbon tetrachloride reacts additively with β -pinene at refluxing temperature in the presence of benzoyl peroxide to give 7-dichloromethyl-8-chloro- Δ -*p*-menthene in 97% yield:⁴⁹⁵



Bromotrichloromethane is known to react toward unsaturated compounds in a similar manner. The compound is more reactive than carbon tetrachloride, and gives addition products in good yield with such olefins as allyl chloride and octene-2, with which carbon tetrachloride reacts only to a very limited extent. It gives an addition product in good yield with styrene, whereas carbon tetrachloride gives only polymeric bodies with this compound. Carbon tetrabromide adds to olefinic double bonds in much the same manner as carbon tetrachloride. It gives an addition compound with styrene in almost quantitative yield. One may assume that other bromochloromethanes are capable of reacting additively with olefins.²¹⁸

The reaction is considered to involve thermally generated free radicals and may conceivably proceed as follows:



The last three reactions form the succeeding steps in the chain reaction set in motion by radicals generated by the thermal dissociation of the peroxide.

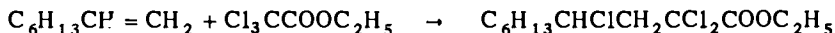
The addition reaction predominates only if R is an aliphatic group, otherwise polymeric compounds result as the main product. Ethylenic compounds in which a CCl_2 or CCl_3 group is adjacent to the double bonds undergo the reaction. Methylene chloride and chloro ethanes also add to ethylenic compounds, although reaction proceeds more slowly than with carbon tetrachloride or chloroform. Chloropropanes with a small number of chlorine atoms in their molecule do not add at double bonds, but pentachloropropane is capable of undergoing the reaction.²¹⁹

Carbon tetrachloride and chloroform react additively with vinyl chloride and dichloroethylene in the presence of aluminum chloride.⁴⁹⁶

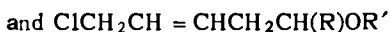
Chloroacetic acids react with olefins in the presence of diacetyl peroxide.⁴⁹⁷ Reaction with dichloroacetic ester and octene-1 proceeds as follows:



With trichloroacetic ester, 1,1,3-trichlorocaproic ester is formed:

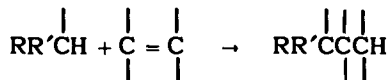


α -Chloro ethers have been added to butadiene in the presence of zinc chloride, and a mixture of unsaturated halo ethers have been obtained in 61 to 86% yield:⁴⁹⁸



Reaction of Olefins with Organic Compounds with a Reactive Methylene Group; Michael's Condensation.⁴⁹⁹

Certain unsaturated compounds are capable of reacting additively with compounds containing a reactive methylene group in the presence of appropriate catalysts. The general reaction may be represented as follows:



The reaction, which is known as the Michael condensation, takes place when the unsaturated bond is activated by one of the groups COOR, COR, CN, CONH₂, NO₂, SO₂R, CHO. The methyl group is also activated by these groups and by aromatic residues. Compounds with reactive acetylenic bonds, and quinone react in the same manner as olefinic bodies.⁵⁰⁰ One or both participant compounds may be vinylogs.⁵⁰¹

Secondary amines are effective catalysts for the Michael condensation. They seldom cause reactions other than the normal. They give satisfactory results in cases in which ring closure, rearrangements or the formation of trimolecular compounds are to be avoided. Amines are comparatively mild catalysts, however, and it is often necessary to heat the reaction mixture under reflux for a long period when amines are employed as catalysts. In many instances they fail to bring about the reaction.

Sodium alkoxides also promote the Michael condensation and are considerably more vigorous catalysts than secondary amines, and are often capable of bringing about reactions that fail to proceed in the presence of amines. The amounts of alkali metal alkoxides usually employed in the Michael condensation are 1/6 to 1/3 molecular equivalent. As a rule the reaction mixture is allowed to remain at room temperature for a period varying between twenty to one hundred and fifty hours, depending on the nature of the reactants. Higher temperatures must be avoided, since they favor regression and side reactions. Higher temperatures are permissible if the ultimate aim is the preparation of cyclic bodies or trimeric compounds.

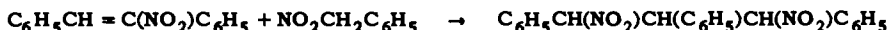
The condensation may be carried out by first preparing the sodio derivative of the reactive methylene compound by use of metallic sodium or sodamide, then causing this to react with the olefinic body.⁵⁰² Benzene, ether, dioxane and alcohols have been used as solvents. The use of alcohols as solvents involves the possibility that the alcohol rather than the compound with the reactive methylene group reacts with the olefin. This occurs, for example, when an attempt is made to condense benzyl cyanide with methyl acrylate or acrylonitrile in alcoholic solution, when addition of the alcohol to the double bond takes place in preference to the Michael condensation.⁵⁰³

Among unsaturated compounds, ketones undergo the condensation more readily than the corresponding ester, and this more readily than the nitrile. Replacement of the hydrogen atoms of the ethylenic group in the unsaturated compound

by alkyl, aryl, carbethoxy, or acyl groups causes a decrease in the reactivity of the double bond. The magnitude of the effect would seem to increase with the size of the substituent. Negative groups such as COOR and CN appear to exert an activating influence which may counteract more or less their steric effect. Among nitro substituted benzene groups, the para isomer exerts a greater deactivating influence than the ortho isomer.

While ethyl cinnamate fails to react with anthrone, ethyl benzalmalonate gives a condensation product in good yield.⁵⁰⁴ Acetophenone and ethyl cinnamate yield β -phenyl- β -benzoylbutyric ester, $C_6H_5OCOCH_2CH(C_6H_5)CH_2COC_6H_5$.⁵¹⁸

Nitromethane has been condensed with ethyl cinnamate to ethyl 2-phenyl-2-nitromethylpropionate.⁵⁰⁵ An addition compound has been obtained similarly with *secondary nitropropane* and benzylideneacetophenone.⁵⁰⁶ The methyl group in *phenylnitromethane* is reactive and undergoes the Michael condensation with certain olefinic compounds. Thus, a dinitrotriphenylpropane is obtained with 1,2-diphenylnitroethylene:

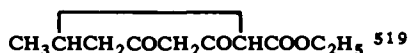


Sodium nitroalkanes react additively with α , β -unsaturated ketones, esters and nitroalkenes:²²⁰



Treatment with acids converts the resulting addition products to nitro compounds.

Ethyl sodioacetoacetate reacts with crotonic ester to form methylhydroresorcylic acid ester,



Other α , β -unsaturated esters react in a similar manner:

The peroxide catalyzed addition of aldehydes to unsaturated esters and ketones yields keto esters and diketones difficult to prepare by other methods.⁵⁰⁷ Acetylsuccinic ester has been prepared, for example, from acetaldehyde and ethyl maleate.

Reaction of Olefins with Halo Silanes

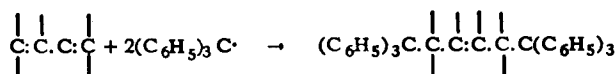
Trichlorosilane reacts smoothly and nearly quantitatively with 1-octene in the presence of diacetyl peroxide:⁵⁰⁸



The reaction is applicable to various other olefins. Ultraviolet light and high temperatures accelerate the reaction.⁵⁰⁹

Reaction of Olefins with Organic Radicals

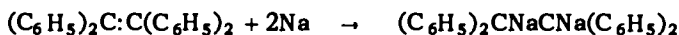
The triphenylmethane radical is capable of adding at unsaturated bonds, the compound giving a 1,4-addition product with conjugated dienes:



Vinyl acetylene reacts similarly.²²¹

Addition of Alkali Metals to Ethylenic Bonds

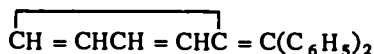
Purely aliphatic compounds with one double bond do not generally add alkali metals; addition takes place when aromatic groups are attached to the unsaturated carbon atoms, or when more than one olefinic linkages in conjugated position are present in the molecule:²²²



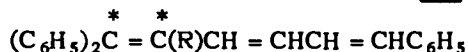
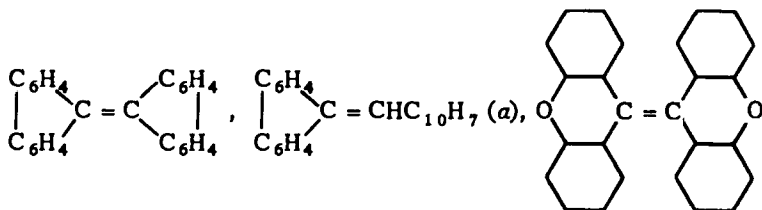
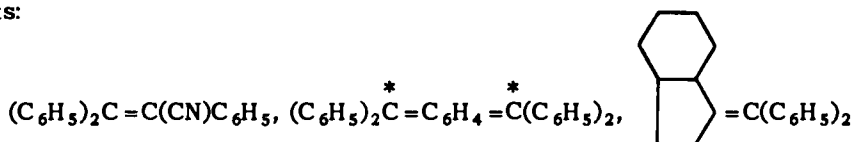
Bis-isobutene ethylene, $[(\text{CH}_3)_2\text{C}=\text{CH}]_2\text{C}=\text{CH}_2$, gives with sodium the compound $[(\text{CH}_3)_2\text{C}=\text{CH}]_2\text{CNaCH}_2\text{CH}_2\text{CNa}[\text{CH}=\text{C}(\text{CH}_3)_2]$.

The metal is employed in the finely divided or "colloidal" form, suspended in ether or other suitable medium, and the reaction is carried out under an atmosphere of nitrogen.²²³ The reaction may be carried out also with the liquid sodium-potassium alloy,²²⁴ and with an alkali metal dissolved in liquid ammonia.²²⁵

Styrene, propenylbenzene, Δ , -dihydronaphthalene, di-, tri- and tetraphenylethylenes are capable of adding sodium; polynuclear hydrocarbons, such as diphenyl, naphthalene, anthracene, and phenanthrene also add alkali metals. Addition takes place at the double bond outside of the ring in the fulvene,



The following compounds also add sodium, asterisks indicating the point of attachment of the metal where more than one possible mode of attachment exists:



Sodium addition to polyphenylated open chain hydrocarbons takes place at 1 and 4 positions. Sodium adds to tetraphenylallene to form a compound which, according to Schlenk and Bergman, contains a new type of divalent carbon and has the structure $(\text{C}_6\text{H}_5)_2\text{CLi} \cdot \text{C} \cdot \text{CLi}(\text{C}_6\text{H}_5)_2$.²²⁶

The ability of ethylenic compounds to react with alkali metals is the more pronounced, the smaller the "residual affinity"(*) at the double bond.²²⁷ The ad-

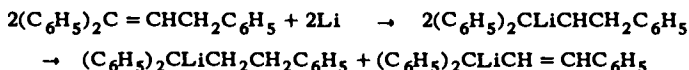
(*)It should be noted that estimates of "residual affinity" are based on observed reactivity toward halogens, oxidizing agents and other reagents of primarily "electronegative" character.

dition of sodium takes place more readily, for example, at the double bond in tri- and tetraphenylethylene than that in stilbene, the rule applying also to fulvenes. Methylation at the α -position in styrene enhances the tendency of the double bond to react with sodium, while methylation at the β -position has the opposite effect. Alcoylation of diphenylethylene at the β -position renders the addition of sodium more difficult. Mono- and dimethylstilbenes add sodium more readily than stilbene. Sodium reacting with benzal- and anisalfluorenes causes cleavage of the molecule, but with α -naphthylidene fluorene, addition takes place without cleavage.²²⁸ Diphenyldimethylethylene, $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}(\text{CH}_3)_2$, does not react either with sodium or with potassium, but it reacts with an alloy of potassium and sodium containing 1 part of the former and 2 of the latter, to form the potassium addition compound $(\text{C}_6\text{H}_5)_2\text{CKCK}(\text{CH}_3)_2$.²²⁹

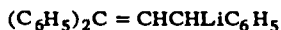
Olefinic compounds which readily add alkali metals react with difficulty with halogens. Thus, tetraphenylethylene, which readily combines with sodium, reacts incompletely with chlorine, and fails to react with bromine.

Olefins which readily add sodium are reduced with sodium amalgam and alcohol. The product of hydrolysis of the sodium addition compounds of dienes are not necessarily identical with the product obtained by the partial reduction of the diene with hydrogen.

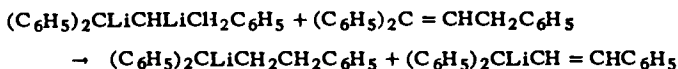
Disproportionation reactions occasionally take place in the course of the reaction of alkali metals with unsaturated compounds. Thus, potassium reacting with 1,1-diphenyl-2,2-dimethylethylene gives two compounds, $\text{C}_{16}\text{H}_{17}\text{K}$ and $\text{C}_{16}\text{H}_{15}\text{K}$. Lithium reacting with diphenylbenzylethylene also yields two products which are apparently formed in the following manner:²³⁰



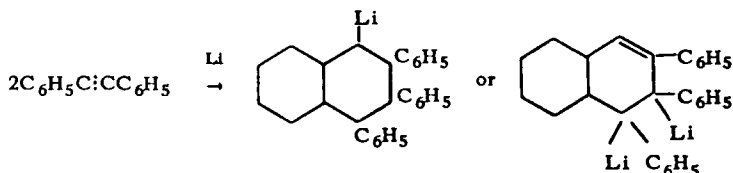
The second compound then undergoes molecular rearrangement to form



The reaction may also be explained, however, by assuming the formation of the dilithium addition compound and the subsequent reaction of this with the original olefin:



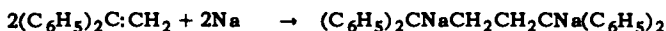
Two molecules of tolan combine under the action of lithium to form the lithium derivatives of triphenyl naphthalene:²³¹



Lithium adds to tetraphenylallene to form the compound

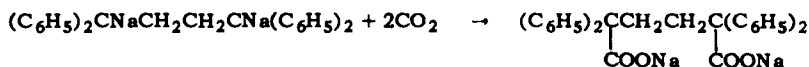


Alkali metals may cause the dimerization of certain olefinic compounds. Thus, *unsym-diphenylethylene* is converted to disodium tetraphenylbutane under the action of metallic sodium:²²⁸



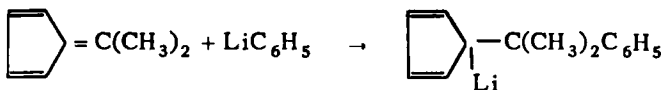
The alkali metal derivatives of such dimeric olefins are reconverted to the original monomeric olefins by treatment with mercury.

The alkali metal addition products of olefins react with carbon dioxide to form the alkali metal salts of dicarboxylic acids:



Reaction of Alkali Metal Alkyls and Organomagnesium Halides with Olefins

Alkali metal alkyls add at a conjugated double bond, or a double bond in the vicinity of an aromatic group:²³²

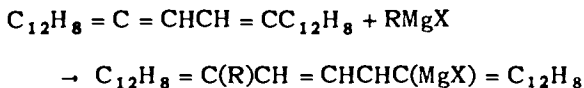


Highly phenylated olefins fail to react, although the fluorene ring appears to facilitate addition.²³¹ The reaction takes place also with certain polycyclic aromatic hydrocarbons such as anthracene.

Polymerization takes place if the addition product itself is capable of reacting with the olefin.

Simple alkali metal alkyls such as lithium ethyl, -propyl, -butyl and -phenyl, as well as colored compounds of the type of $\text{KC}(\text{CH}_3)_2\text{C}_6\text{H}_5$ give addition products. The ease of reaction is determined by the nature of the group attached to the metal and of the groups present in the ethylenic compound. Phenyllithium, benzylsodium and phenylisopropylpotassium react readily but triphenylmethanesodium reacts with difficulty. Lithium compounds react less readily than sodium derivatives. The solvent has a marked effect on the rate of addition, reaction being complete in some instances in ether within a few minutes, but requiring a few days for its completion when carried out in benzene.

Addition reactions have been reported between organomagnesium compounds and certain unsaturated bodies. Such an additive reaction has been observed, for example, between *tert*-butylmagnesium chloride and *o*-bibenzyleneethylene, and between Grignard reagents and 1,4-di-*o*-biphenylene-1,3-butadiene:⁵⁶⁵



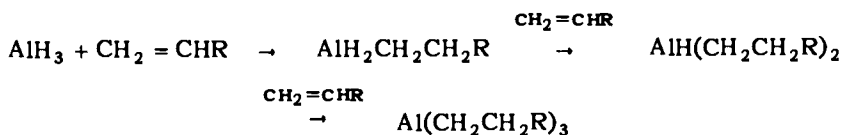
Condensation reactions of a similar type have been observed with bibenzofulvene, 2,3-diphenylbenzofulvene and 1,2,3,4-tetraphenylfulvene.⁵⁶⁶

Reaction with Mercuric Salts

Unsaturated compounds are capable of reacting with mercuric salts, especially with mercuric acetate, to form organomercury compounds. The subject is dealt with in Chapter 15.

Addition of Aluminum- and Organoaluminum Hydrides

Aluminum hydride adds readily to ethylene and other unsaturated compounds with an olefinic bond at the end of a chain.⁵⁶⁷ The adducts are never free from etherates since aluminum hydride is prepared in ethereal solution and can never be completely freed from the solvent. Mono- and dialkylaluminum hydrides also react additively with 1,2-olefinic compounds, so that the final product of the reaction of aluminum hydride and an 1,2-olefin is a trialkylaluminum, providing three molecular equivalents of the olefin are present in the reaction mixture:

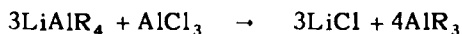


Lithium aluminum hydride is also capable of undergoing an additive reaction with 1,2-olefins:



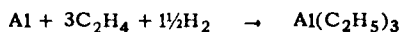
All hydrogens in the compound are replaceable with the alkyl group $-\text{CH}_2\text{CH}_2\text{R}$ by successive reaction with additional molecules of the olefin.⁵⁶⁸ The reaction of lithium aluminum hydride with olefins proceed less readily than that of aluminum hydride; it proceeds at a good rate a little above 100°.

Aluminum chloride reacts with lithium aluminum tetraalkyls forming lithium chloride and an aluminum trialkyl:

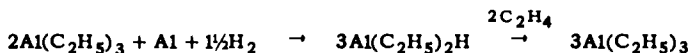


Since lithium aluminum tetraalkyls may be prepared free from ether, this reaction offers the possibility of preparing aluminum trialkyls in the ether-free condition.

Aluminum alkyls may be prepared directly from metallic aluminum by reaction with ethylene or monosubstituted ethylenes and hydrogen at about 120°.⁵⁶⁹



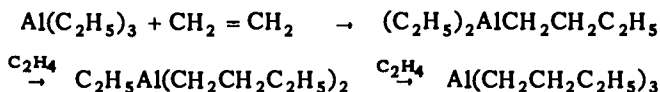
In this reaction the intermediate aluminum mono and dialkyls are formed together with aluminum trialkyls, even when three equivalents of the ethylenic compound are employed to one of aluminum. It is possible, however, to obtain the trialkyl compound as the principal product by an indirect route, involving the reaction of two molecular equivalents of an aluminum trialkyl with one of aluminum and one and a half molecular equivalents of hydrogen, and condensation of the resulting dialkylaluminum hydride with the olefin:



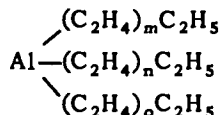
Aluminum alkyls are readily oxidized to alcoholates, which may be decomposed to alcohols. This fact makes possible the preparation of primary alcohols from olefins $\text{RCH} = \text{CH}_2$, a feat which is not possible by other available methods.

It should be borne in mind that *diethylaluminum hydride* ignites spontaneously on exposure to air, and reacts violently with water, alcohol, etc. The compound distills undecomposed at $55-56^\circ$ under the highest vacuum obtainable, but occasionally may undergo disproportionation into aluminum triethyl and aluminum hydride, the latter undergoing decomposition. Diethylaluminum hydride appears to be stable, however, even at $160-180^\circ$.

Aluminum trialkyls are capable of reacting additively with ethylene:

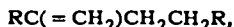


The reaction takes place at 100 to 120° , while the condensation of alkylaluminum hydride with ethylene proceeds at 60 to 80° .⁵⁶⁷ In the equations above, a select three have been given of a large number of possible reactions that proceed consecutively or simultaneously. The end result is a mixture of a large number of compounds that may be represented by the general formula:

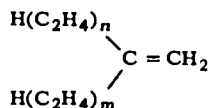


assuming one starts with aluminum triethyl. Decomposition of the addition compounds with water yields the hydrocarbons $\text{H}(\text{C}_2\text{H}_4)_m\text{C}_2\text{H}_5$, $\text{H}(\text{C}_2\text{H}_4)_n\text{C}_2\text{H}_5$ and $\text{H}(\text{C}_2\text{H}_4)_o\text{C}_2\text{H}_5$, which may be separated by fractionation. The method lends itself to the preparation of very high molecular saturated hydrocarbons.

It is possible to induce the strictly catalytic polymerization of ethylene at about 200° with a small amount of aluminum trialkyl. At this temperature aluminum alkyls undergo dissociation into an olefin and an aluminum hydride. It may be assumed therefore that underlying the catalytic effect and continually at work is a process of combination and dissociation. 1,2-Olefins other than ethylene are converted to dimers



and for this reason the final condensation product is made up of a mixture of molecules of the type

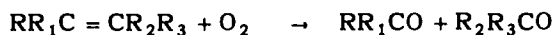


The process is complicated by the fact that many olefinic bodies undergo molecular rearrangements under the conditions of the reaction.

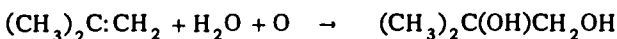
It is possible to convert ethylene to butene by simple passage of the gas at 180 to 200° under moderate pressure through aluminum triethyl. Butene may be converted to butadiene in good yield by dehydrogenation.

Oxidation of Olefins

Many oxidizing agents attack olefinic compounds at the point of unsaturation, and cleavage at this point is the final result of the reaction when oxidation is sufficiently vigorous. Union of each of the unsaturated carbons with an oxygen atom may take place if the oxidation is conducted under properly controlled conditions, and the final result may be the formation of two carbonyl compounds



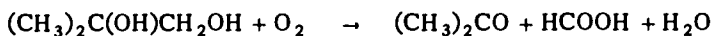
The reagent most commonly used for the oxidation of unsaturated compounds is aqueous *potassium permanganate*. A cold neutral solution of this compound usually gives a glycol as the first product of oxidation:²³³



The general procedure²³⁴ is to add a cold dilute solution of the permanganate in slight excess slowly to the unsaturated compound. The latter, if insoluble in water, may be placed in acetone solution. After completion of the reaction the precipitated manganese dioxide is filtered off, the filtrate is neutralized with dilute sulfuric acid or by saturating with carbon dioxide; it is then concentrated by evaporation, and the glycol is isolated and purified. If the glycol is miscible with water, it is separated from the latter by extraction with ether.

Alicyclic compounds with an ethylenic linkage give a *cis*-glycol when treated with permanganate, whereas peracids give rise to the *trans* compound.

More vigorous oxidation causes severance of the carbon to carbon bond, usually at the point where unsaturated bonds were originally present:



Pinonic acid is the final product obtained from the permanganate oxidation of α -pinene.²³⁵ Rupture of the carbon to carbon bond may take place at points other than that occupied by the multiple bonds, as, for example, in the case of carvenone and terpineol-4.

If several isolated double bonds are present in the molecule, tetrahydric alcohols or diglycols are usually obtained. On the other hand, conjugated double bonds cannot, as a rule, be hydroxylated simultaneously, cleavage of the molecule at one double bond occurring, while addition of two hydroxyl groups takes place at the other. In certain cases, however, erythrol derivatives are obtained with four adjacent hydroxyl groups.

Olefins can also be converted to glycols by the action of a glacial acetic acid solution of *hydrogen peroxide*.⁵¹⁰ Reaction proceeds rapidly and quantitatively at 40° in the presence of catalytic quantities of sulfuric acid. Glyceryl esters may be obtained by this method, from allyl esters. Many unsaturated compounds are rapidly hydroxylated by *performic acid*. Trans addition of the hydroxyl groups takes place. Oleic acid is converted to 9,10-dihydroxystearic acid by this treatment at room temperature.⁵¹¹ No epoxy compound is obtained by this treatment, although it is possible that an epoxide is the initial product of the reaction.

Performic acid is readily formed by mixing 98 to 100% formic acid with 90% hydrogen peroxide containing a trace of sulfuric acid.⁵¹²

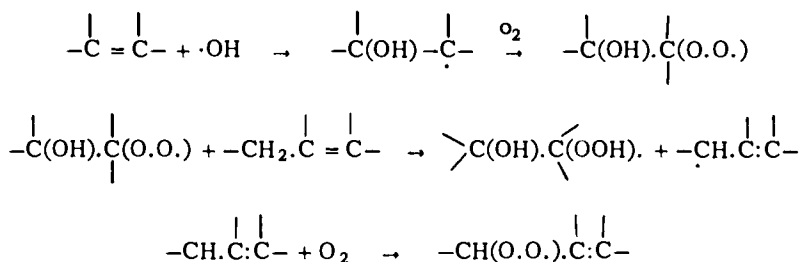
Hydroxylation may be brought about with hydrogen peroxide in *tert*-butyl alcohol in the presence of osmium tetroxide.⁵¹³ The yields of diols range from 30 to 60%. *Cis* addition of the hydroxyl groups takes place. The catalyst is volatile and dangerous to handle. It is conveniently used in solution in *tert*-butyl alcohol. Selenium dioxide and pertungstic acid cause the *trans* addition of the hydroxyl groups. Conversion of olefins to glycols may be brought about, furthermore, by treatment with aqueous sodium chlorate or silver chlorate containing a little osmium tetroxide,²³⁶ with mercuric acetate,²³⁷ and lead tetraacetate.²³⁸ Oxidation with chromic acid usually results in cleavage of the double bond without the formation of the intermediate glycols.

The reaction of olefins with peracids results in the formation of oxido compounds. Reaction with hydrogen peroxide also yields oxido compounds. Since oxido compounds are in reality internal ethers, the subject has been taken up in connection with ethers, Chapter 2. Perbenzoic acid does not attack double bonds conjugated with a carbonyl group. Ethyl fumarate and maleate, treated with this reagent, are polymerized. Diallyl shows an exceptional behavior and is converted to a furan derivative on treatment with perbenzoic acid.⁵¹⁴

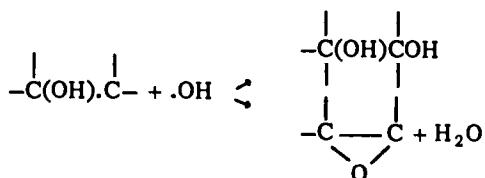
Reaction of Olefins with Oxygen

Oxygen reacts at moderate temperatures with certain olefinic compounds, adding at an α -carbon bearing a hydrogen atom, with the formation of a hydroperoxide, ROOH, which retains the original olefinic double bond. Conversion to a hydroperoxide takes place quantitatively with non-conjugated olefins capable of reacting with oxygen.²³⁹ Reaction may be brought about by exposing the compound in a thin film to oxygen, or by shaking it with oxygen until absorption of the gas ceases.

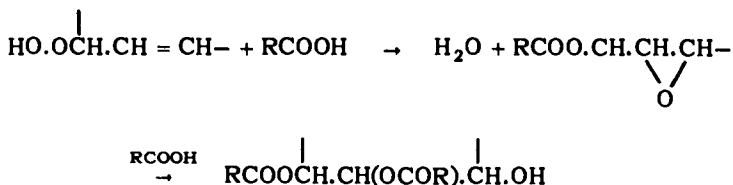
At temperatures in excess of 100°, the hydroperoxide apparently decomposes, releasing hydroxyl radicals which are capable of adding at the double bonds, forming hydroxylated radicals; these in turn react with molecular oxygen, finally yielding a saturated hydroxy hydroperoxide. It is probable that the reaction takes place by the following steps:



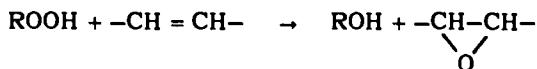
A glycol or an oxide also result by chain-breaking side reactions such as



When the autoxidation of olefins is carried out in the presence of acids, triols or their esters are formed, the reaction probably proceeding from the hydroperoxide stage in the following manner:²⁴⁰



Simple epoxides may also be formed in the process as follows:



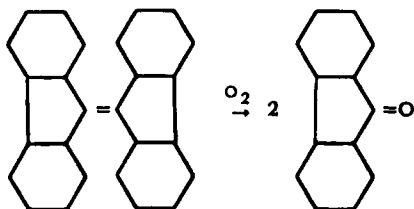
degradation of the oxide yielding ketones or α -glycols or products resulting from the oxidation of these compounds.

Crotonaldehyde is converted principally to crotonic acid when subjected to the action of oxygen in acetic acid solution. Manganese ions act as a catalyst, 0.00001% being the optimum concentration at 20°. ⁴¹¹

The susceptibility of olefins to attack by oxygen is dependent upon the character of the compound. Aliphatic unsaturated compounds are usually stable toward oxygen, while conjugated dienes and polyenes are susceptible to attack. In general, negative substituents asymmetrically situated with respect to the double bond enhance the tendency to oxidation. Cyclic unsaturated compounds such as cyclohexene, 1-methyl and 1,2-dimethylcyclohexene are susceptible to attack. Oleic acid, methyl elaidate, ethyl linoleate and many polyisoprenes such as squalene, dihydromyrcene and raw rubber are capable of reacting with oxygen. The primary product formed with all of these compounds is a hydroperoxide; these hydroperoxides often break down rapidly as the reaction proceeds. ²⁴¹

Ergosterol undergoes oxidation in the presence of fluorescent dyes to form a fairly stable peroxide; ²⁴² the acetate similarly yields a peroxide. These peroxides are readily reduced with sodium and alcohol, and give color reactions with arsenic and antimony chlorides similar to those obtained with vitamin A.

Compounds in which there is a double bond connecting carbon atoms forming part of aromatic rings often react readily with oxygen with severance of the carbon bonds. Thus, diphenyleneethylene (*Graebe's hydrocarbon*) in ethereal solution, exposed to the action of air, yields fluorenone:



Migration of a substituent, especially of halogens, may take place during the autoxidation of unsaturated compounds;²⁴³ α -bromostyrene, $\text{C}_6\text{H}_5\text{CBr}=\text{CH}_2$, for example, is converted to bromacetophenone, $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$ on oxidation.

Isomerization of Unsaturated Compounds

The position of the double bond in most unsaturated compounds may be changed under the action of alkaline and acid reagents at the appropriate temperature. It may be stated generally that the molecule tends to assume a symmetrical arrangement, ethylacetylene, for example, changing to dimethylacetylene. The multiple bond usually shifts toward certain substituents; thus, methylchavicol,

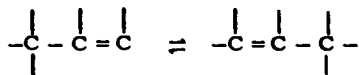


is converted to anethole,



and methyl allyl ketone to methyl propenyl ketone. (*)²⁴⁴ Similar transformations are also observed with methyleugenol, isosafrole and apiole. A shift of this kind may be considered to occur during the dehydration of inactive amyl alcohol, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH}$, which results in the formation of trimethylethylene.²⁴⁵ Negative substituents appear to "attract" the double bond. These generalizations do not hold unfailingly, however, if the compound is of a complex nature.

The isomerization of olefinic bodies is traceable to the tautomerism of these compounds. A condition of equilibrium prevails between the two tautomeric forms:

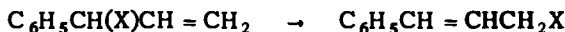


The equilibrium is sensitive to substitution in certain positions of the three carbon system. In unsaturated ketones containing the grouping $\text{C}=\text{C}=\text{C}.\text{CO}$, the α , β -unsaturated form is the stable configuration when the γ -position is not substituted, as is the case with crotonic acid, β , β -dimethylacrylic acid, β -methylcinnamic acid and isopropylidene ketones. The introduction of a single methyl group into the γ -position causes the equilibrium to shift in the direction of the β , γ -unsaturated form.⁵¹⁵ The effect of alkyl groups in the γ -position decreases with increase in the chain length. The carboxyl, carbethoxy, and cyano groups in the α - or γ -positions increase the instability of the

(*)Propylene derivatives are distinguished from the isomeric allyl compounds by their higher specific gravities, higher melting points and greater refractive power.

unsaturated linkage.⁵¹⁶ The effect of a carboxyl or carboxy group in the β -position is to favor the β, γ -form.

In compounds $C_6H_5CH(X)CH = CH_2$ the isomeric change

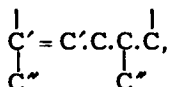


takes place with difficulty if X is OH, but proceeds readily if X is OCOR. The change takes place with extreme ease if X is Br. The ease of isomerization of compounds $RCH(X)CH = CH_2$ to $RCH = CHCH_2X$ is influenced by the nature of R. The magnitude of the effect of various groups is in the order



If more than one double bond is present in the molecule of an unsaturated compound, there is a tendency toward the formation of a conjugated system.

If a junction is effected between the double primed carbon atoms in the system

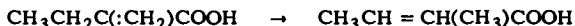


the double bond between the primed carbon atoms migrates to another position in the ring, away from the twice primed carbon atoms (*Bredt's rule*).²⁴⁶

The rearrangement of allylbenzene and allylphenyl ethers is brought about readily by boiling with aqueous alkalis.

A shift of the double bond in α, β - and β, γ -unsaturated acids and ketones takes place under the influence of alkalis and various amines;²⁴⁷ isomerization of β, γ -unsaturated ketones is usually brought about by acid reagents. An equilibrium is established between the α, β - and β, γ -forms when potassium hydroxide or sodium ethoxide are used as catalysts.²⁴⁸

Treatment with hot sulfuric acid may cause the migration of the multiple bond in compounds unaffected by cold dilute sulfuric acid. Certain α, β -unsaturated acids may undergo isomerization by this treatment. Thus, unsaturated bonds in a short chain may migrate into a longer chain:



The double bond may migrate further in the longer chain, to the β, γ -position, for example, and ultimately a γ -lactone may be formed.

A shift in the position of a double bond is common in the *terpene series*, and is frequently induced by acids. The double bond in a side chain generally migrates toward or into the nucleus.²⁴⁹

Halo olefins of the type $RCH = CH.CHXR'$ are partially isomerized on heating to $RCHXCH = CHR'$.²⁵⁰

Δ^2 -Dihydronaphthalene is transformed into Δ^1 -dihydronaphthalene under the influence of alkalis.²⁵¹

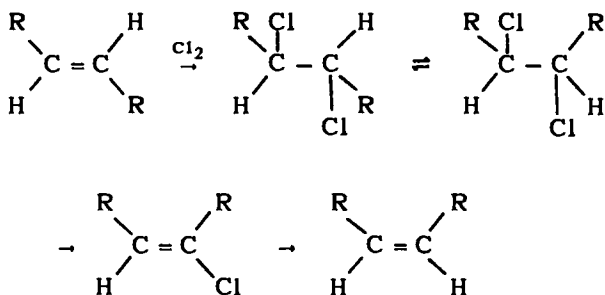
Ethylmethylacetylene, $C_2H_5C \equiv CCH_3$, is converted to sodium *n*-propylacetylide, $CH_3CH_2CH_2C \equiv CNa$, by the action of metallic sodium. Sodium amide forces the migration of a multiple bond farther toward the end of a chain.²⁵²

Isopropylacetylene subjected to the action of alcoholic potassium hydroxide is converted to dimethylallene, $(CH_3)_2C = C = CH_2$. The latter may be reconverted to isopropylacetylene under the action of metallic sodium. γ -Methyl- Δ^2 -butene,



is partially isomerized to γ -methyl- Δ^2 -butene, $(\text{CH}_3)_2\text{C} = \text{CHCH}_3$, when it is passed over alumina heated at $525\text{--}535^\circ$.²⁵³

Trans isomerides of olefinic compounds have been converted to *cis* isomers by a three-step process which involves chlorination of the olefin, dehydrochlorination to the unsaturated monochloro derivative, and reduction of the latter with sodium in liquid ammonia:⁵¹⁷



Polymerization of Unsaturated Compounds

The lower members of the normal olefin series show little tendency toward polymerization; this is especially true of ethylene, the successful large scale polymerization of which is an accomplishment of recent date. Polymerization may be promoted by certain catalysts; many olefins polymerize, for example, under the influence of sulfuric acid²⁵⁴ or zinc chloride,²⁵⁵ although ethylene is not polymerized by these reagents.²⁵⁶ Isobutylene gives diisobutylene, isoamylenes yield di-, tri- and higher isoamylenes. The polymers themselves are unsaturated compounds containing double bonds.

Aluminum chloride and bromide also induce the polymerization of olefins, ethylene forming with the latter compound a complex, $\text{AlBr}_3\text{C}_4\text{H}_{18}$, which, when decomposed by water, gives hydrocarbons of low volatility.²⁵⁷ Higher olefins, such as amylene and hexylene, are converted to cycloparaffins under the influence of aluminum chloride.²⁵⁸ Aluminum hydride, alkyl aluminum hydrides and aluminum alkyls may also induce polymerization of ethylene and other olefins.⁵⁶⁷ Boron trifluoride is an effective catalyst of polymerization and it is claimed to induce the polymerization of ethylene and propylene.²⁵⁹ Finely divided metals, such as powdered nickel, also promote the polymerization of unsaturated compounds.

Substituents in the molecule of an olefin hydrocarbon may increase the tendency toward polymerization to a great extent. Aromatic groups, oxygenated radicals, and halogens exert a marked influence. The accumulation of a large number of such substituents in the molecule may exert a hindering influence, however, and certain highly substituted olefins polymerize very slowly, if at all. Oxygen and peroxides in minute amounts play a dominant role in many processes of polymerization.²⁶⁰

Isobutylene polymerizes readily in the presence of a variety of catalysts, boron trifluoride, and aluminum- and titanium chlorides being among the most effective.²⁶¹ Polymerization takes place with almost explosive violence in the presence of boron trifluoride,²⁶² and polymers with a molecular weight in excess of 400,000 may be prepared. It is of interest to note that diisobutylene and triisobutylene cannot be catalytically polymerized to high molecular products.

Ordinary amylene polymerizes readily;²⁶³ it yields diamylene when treated with sulfuric acid diluted with an equal volume of water, dimerization taking place even at 0°. Polymerization with zinc chloride results in the formation of a certain amount of triamylene.

Tetrafluoroethylene and trifluorochloroethylene polymerize under pressure in the presence of benzoyl peroxide to high molecular compounds, which withstand the action of most highly reactive chemical reagents and of boiling acids.⁴¹² Trifluorochloroethylene has also been condensed under partially controlled conditions to liquid polymeric substances.⁴¹³

Ozonization of Unsaturated Compounds

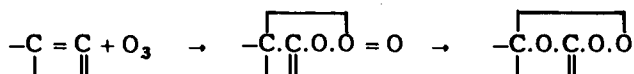
Preparation of Ozonides

Ozone reacts with unsaturated compounds to give addition products,²⁶⁴ the so-called ozonides. The unsaturated bond takes up one molecule of ozone, although prolonged ozonization may lead to the formation of perozonides.

Harries, whose work greatly contributed to the knowledge of the subject, assumed that three atoms of oxygen are combined with the two unsaturated

carbon atoms, as follows, $\begin{array}{c} \text{---C---C---} \\ | \quad || \\ \text{---C---C---O---O---O---} \end{array}$. The behavior of ozonides seems to be

in harmony, however, with the structure proposed by Staudinger, $\begin{array}{c} \text{---CO---CO---} \\ | \quad || \\ \text{---O---} \end{array}$, addition being assumed to proceed in two stages:²⁶⁵



The intermediate compounds shown in this equation have been termed molozonides, the final products isozonides.

The ozonization reaction has assumed importance, since it serves to determine the position of the double bond in unsaturated compounds. For, decomposition of ozonides by various methods results in the formation of carbonyl compounds or a carbonyl compound and a carboxylic acid, with cleavage of the molecule at the point where the unsaturated bonds were originally located. Identification of the compounds formed as a result of the decomposition of the ozonides often unequivocally determines the position of the unsaturated bonds.

The general procedure followed in carrying out the ozonization of unsaturated compounds is to conduct dry ozonized air or oxygen of the appropriate ozone content

through a solution of 1 to 4 gm of the unsaturated compound in chloroform, carbon tetrachloride, or other suitable solvent cooled in ice. The concentration of ozone employed varies between 1 and 15%, depending upon the compound treated. The use of dry oxygen with an ozone content of 8-10% is satisfactory in many cases.²⁶⁶ A rate of flow of 4.7 liters per minute of the ozonized oxygen is found to give satisfactory results with many compounds.

In order to assure good contact between the solution and ozonized gas, the latter is bubbled through a fritted glass distributor.²⁶⁷ The countercurrent flow principle has also been used successfully, the solution of the unsaturated compound being made to run down as a film through a tower packed with small glass rings, while the ozonized gas rises up through the column.

After the completion of ozonization, the ozonide may be isolated by evaporation of the solvent under reduced pressure. Evaporation may be carried out at 20° under vacuum. A small sample should first be evaporated in this manner in order to determine the possibility of explosion, since some ozonides explode at or little above room temperature. In dealing with highly explosive ozonides, evaporation may be carried out at a low temperature.

Ozonides, as thus isolated, generally are oils or semi-solid bodies. They may be partially purified by washing with liquids in which they are insoluble or slightly soluble. Ozonides of some low molecular compounds, such as ethylene, butylene, etc., may be purified by cautious distillation. Some may also be partially purified by precipitation from their acetic acid or ethyl acetate solutions by the addition of petroleum ether.

The lower olefins and acetylene are ozonized in the gas phase in the presence of inert diluents.⁵³⁷

The ozone required for the reaction may be generated by means of an ozonizer of Henne type.²⁶⁸ The crude ozone, which generally contains some oxozone, is passed through a 5% sodium hydroxide solution and then through sulfuric acid, before being conducted into the solution of the unsaturated compound.

Completion of the reaction may be ascertained by adding a few drops of a solution of bromine in acetic acid to a test portion from the reaction mixture; the bromine color is not rapidly discharged if the reaction is complete. If the reaction is carried out at a low temperature, then a blue color assumed by the solution due to dissolved ozone is an indication of complete reaction. An analysis of the ozonide is, however, the most reliable method for the determination of the end point of the reaction. Such an analysis is always desirable, since it is essential that over ozonization be avoided. With compounds which react slowly with ozone, assuring complete reaction without excessive ozonization is a difficult matter.

Polymeric ozonides are often formed during the ozonization of olefins, and are obtained as gummy or glassy products, and occasionally as crystalline compounds. Their formation is favored when ozonization is carried out at temperatures below 0°. Certain solvents also favor the formation of polymeric ozonides.²⁶⁹ Tendency toward polymerization is most marked with compounds the molozonides of which change to isoozonides with difficulty owing to the fact that the unsaturated linkage forms part of a ring structure.

Among *solvents* that may be employed with satisfactory results are saturated hydrocarbons and their chlorinated derivatives; some oxygenated compounds, such as methanol and acetic acid, are also used occasionally. Almost all solvents are attacked gradually by ozone, chlorinated compounds with release of chlorine, this fact accounting for the presence of chlorinated derivatives of the olefin in ozonides prepared in such solvents. Methyl and ethyl chlorides are comparatively stable toward ozone and are to be preferred for the preparation of the most explosive ozonides. Low boiling ligroin and pure hexane may be used as solvents when the reaction is carried out with low concentrations of ozone. Glacial acetic acid is often used as a solvent and it presents the

advantage that it is not attacked even by concentrated ozone. Ethyl acetate may be used, since it is not attacked as long as any unconverted olefin remains in solution.²⁶⁹ In some cases, as in the ozonization of maleic acid, water has been found a satisfactory solvent. The use of benzene should be avoided, however, since it is slowly attacked by ozone, forming highly explosive ozonides.

No general recommendations can be made as to the type of solvent to use in any particular case. The choice should be made according to the character of the compound to be ozonized. The solvent may have an effect on the type of compound obtained; thus, cyclopentene gives a polymeric ozonide when treated in ethyl chloride, but a monomer results in hexane solution.²⁷⁰ Monomeric ozonides are formed almost invariably in acetic acid solution, while polymer formation is observed in carbon tetrachloride. It should be noted that the former solvent is polar, while the latter is non-polar. In preparing sensitive ozonides, it is desirable to employ a solvent which dissolves the ozonide.

The concentration of the solution may be varied widely, although for most olefins dilute solutions are preferable.²⁷¹ Liquid aromatic compounds may be ozonized without the use of a solvent,²⁷² though the danger of an explosion is then greatly increased.²⁷³

The concentration of the ozone is adjusted according to the type of product to be treated: compounds with conjugated double bonds are ozonized with oxygen containing 14 to 15% ozone,²⁷⁴ while sensitive aldehydes are ozonized with air containing 1 to 5% ozone. A low concentration of ozone, say 1%, should be employed in ozonizing unsaturated bonds in the side chain of an aromatic compound. Ozonized air containing less than 1% ozone attacks only ethylenic bonds and does not affect triple bonds;²⁷⁵ the latter are attacked when ozonized oxygen is used.²⁷⁶

In laboratory scale work 0.5 to 1.0 gm of an olefin may be ozonized within an hour. The rate at which ozonization proceeds varies according to the solvent employed; for example, rubber is readily ozonized in chloroform solution, but is attacked very slowly in acetic acid solution.

Ozonization proceeds quantitatively even with compounds which are attacked slowly by ozone, providing sufficient time is allowed for the reaction,²⁷⁷ compounds with conjugated double bonds, benzene derivatives, polynuclear compounds such as naphthalene and phenanthrene forming exceptions.

All aliphatic derivatives are ozonized more or less readily and yield stable monoozonides. The position and activity of the multiple bond exert an influence on the velocity with which the reaction proceeds. Even the less reactive multiple bonds, such as those in benzal malonic ester and related compounds, which fail to add bromine, are capable of reacting with ozone, whereas double bonds unaffected by substituents in the molecule add ozone very rapidly. The rate of addition is markedly decreased when the double bond is conjugated with carbonyl groups. Three or more phenyl groups or two chlorine atoms attached to the doubly bound carbon atoms also decrease the rate of addition. Where two or more double bonds are conjugated with each other, one double bond adds ozone rapidly, while the others react slowly.²⁷⁸ Of the stereoisomeric forms, the *trans*-isomer adds ozone more readily than the *cis*-isomer.²⁷⁹

Unsaturated cyclic hydrocarbons behave toward ozone much like aliphatic olefins. Limonene readily yields a monoozonide, the isopropenyl side-chain being first attacked, while the double bond in the ring is attacked at a much slower rate.

The three double bonds in aromatic compounds are ozonized by use of a relatively high concentration of ozone. The behavior of polynuclear benzole derivatives parallels their behavior toward halogens; naphthalene, for example, adds two molecules of ozone to form a 1,2,3,4-diozonide. The ability of aromatic compounds to add ozone is influenced by substituents, some benzene derivatives showing no tendency to combine with ozone,²⁸⁰ aniline, for example, undergoing degradation under the influence of ozone.

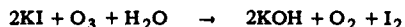
Ozonization has been applied successfully to the determination of the concentration of enol in an enolizable ketone. The determination may be carried out at ordinary temperature, without affecting the enol-ketone equilibrium.⁵²² Ozonization is usually carried out at -20° , the ozonide formed is decomposed in the usual manner and the degree of enolization is calculated from the quantity of the resulting carbonyl compounds or other products of decomposition.

Determination of Ozone

Methods of determination of ozone in air-ozone or oxygen-ozone mixtures depend either on density determinations, or on the estimation of the iodine liberated from an aqueous solution of potassium iodide by the action of ozone.

*Ladenburg's method*²⁸¹ depends on the determination of the density of the ozonized mixture relatively to the unozonized air or oxygen, the ozone content being then calculated from the observed difference.

Schonbein's method is based on the determination of the iodine liberated from a moderately concentrated solution of potassium iodide by the passage of a measured volume of the ozonized gas.²⁸² The liberated iodine is titrated with thiosulfate solution after acidifying the iodide solution with hydrochloric acid. Two atom-equivalents of iodine correspond to one molecule of ozone as is seen from the equation



This method, although only of moderate accuracy, is satisfactory for most purposes.

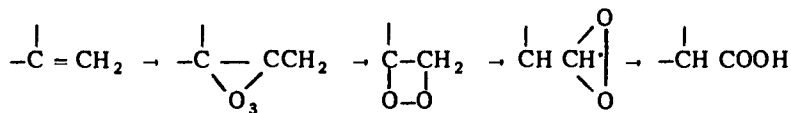
Treadwell and Anneler's modification of *Schonbein's method*, which gives more accurate results, is carried out as follows: A sample of the ozonized air or oxygen is drawn into a gas sampling tube at atmospheric pressure, 10-20 cc of a 5% potassium iodide solution is admitted into the tube, the tube is well shaken and the liberated iodine is titrated with standard sodium thiosulfate solution. The ozone content of the gas may be calculated from the volume of the sampling tube and of sodium thiosulfate solution used in the titration.

Scope and Limitations of Method

Ozonization does not, in general, cause a shift in multiple bonds or other molecular rearrangements and is, for this reason, suitable for the determination of the quantity of enolic modification in equilibrium with ketones.²⁸³ The method has been used successfully to demonstrate the existence of stereoisomerism in unsaturated compounds.²⁸⁴ It has been employed also for the determination of the structure of higher unsaturated fatty acids.²⁸⁵ The structure of rubber and of gutta percha has been successfully established by use of the method.²⁸⁶

In a few exceptional cases ozonization has been observed to induce a change in the structure of the molecule of the compound treated. For example, ozone may cause the appearance of a new double bond after complete ozonization of

the existing unsaturated bonds, as in the case of cholesterol.²⁸⁶ Higher concentrations of ozone may cause dehydration of such compounds as terpineol, with the formation of an unsaturated bond.²⁸⁷ Ozonization of α -fenchene has been observed to result in the formation of a saturated monobasic acid apparently through loss of oxygen and a molecular rearrangement:²⁸⁸



A shift in the position of the double bond due to the effect of ozone, or during the process of decomposition of the ozonide has never been reported.

Amines are not acted upon, in general, by ozone; aliphatic amino acids and acid amide are also unaffected.²⁸⁹ Aromatic amino acids, on the other hand, undergo deep seated changes of an unknown nature, when subjected to the action of ozone.

Peroxides are formed by the action of ozone of a sufficiently high concentration on the carbonyl group of aldehydes and ketones. Thus, nonyl aldehyde gives a labile peroxide melting at 10°. These peroxides are decomposed, however, on treatment with water, with the formation of hydrogen peroxide and the regeneration of the original carbonyl compound.²⁷⁸

Ethyl alcohol and ether yield highly explosive peroxides when subjected to the action of ozone.

Ozone reacts more readily with a carbon to carbon double bond than with one between carbon and nitrogen. As a rule, however, the presence of carbon to nitrogen double bonds in the compound leads to complications which may render the results of ozonolysis inconclusive.

Properties of Ozonides

Ozonides are generally glass-like, colorless compounds or syrupy liquids. They are often amorphous, but a few have been obtained in the crystalline form. Many have a strong, characteristic odor. A few ozonides may be distilled under vacuum without decomposition; among these are 1-phenylbutene-2-ozonide, butylene, propylene and hexylene ozonides.²⁹⁰ These ozonides are volatile at ordinary temperature.

Ozonides, as a general rule, are fairly stable, although many decompose on standing, sometimes explosively. No general rules can be stated in regard to their stability. Most ozonides derived from olefins obtained by the dehydration of tertiary alcohols



containing normal alkyl groups from methyl to amyl, are relatively stable, but those obtained from highly branched and heavier olefins are unstable and decompose on heating or when exposed to light rays.²⁹¹ Diallyl gives a very explosive diozonide. Trichloroethylene ozonide decomposes slowly at as low a temperature as -79°, and explodes violently at room temperature.²⁹² Ozonides of toluene and mesitylene decompose at 0°. ²⁹³

Most ozonides are more or less soluble in many organic solvents, but are insoluble in ligroin. Pinene and cyclooctadiene yield insoluble ozonides. Aliphatic ozonides are soluble in methyl chloride, chloroform, and carbon tetrachloride, but aromatic ozonides precipitate out of these liquids almost quantitatively as thick oils or gelatinous masses.

Almost all ozonides are insoluble in water, but many, nevertheless, undergo decomposition in contact with water.

Polymeric forms of the ozonides have been obtained from compounds having a double bond in a ring, such as cyclopentene, cyclohexene, dicyclopentadiene, dihydrodicyclopentadiene and from aromatic compounds.

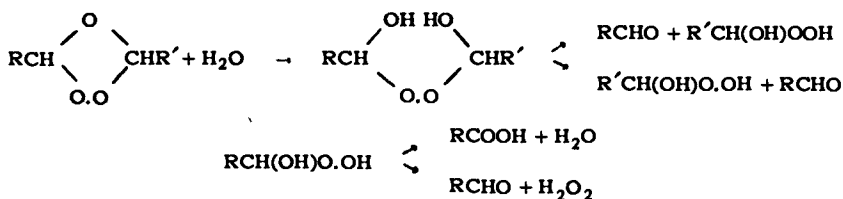
A characteristic property of ozonides is that, like ozone, they exhibit peroxide activity. All ozonides free iodine from potassium iodide; they discharge the color of indigo and of potassium permanganate. They react slowly with bromine, gradually discharging its color. When drops of concentrated sulfuric acid are placed on ozonides they decompose with charring and, occasionally with explosive violence.

Decomposition of Ozonides

Ozonides are decomposed by water to aldehydes or ketones and hydrogen peroxide; they are similarly decomposed on reduction. Decomposition by a suitable method is the next step involved in the determination of the position of multiple bonds in unsaturated compounds.

Decomposition by Hydrolysis

The decomposition of ozonides with water may be considered to take place according to the scheme:²⁹⁴



Decomposition may be brought about by treatment with cold water, or, in dealing with the more stable ozonides, by heating with water under reflux. Almost all ozonides are decomposed when boiled with 10 to 20 times their weight of water; only hydroaromatic ozonides remain unchanged by this treatment. Ozonides of doubly unsaturated hydrocarbons are easily hydrolyzed; ozonides of oxygenated aliphatic compounds, in general, are also readily hydrolyzed, as are those of benzal type compounds and their oxygenated derivatives.

Ozonides of higher aliphatic unsaturated hydrocarbons and of hydroaromatic hydrocarbons are comparatively stable; some are not decomposed by water, while others are only decomposed on prolonged heating with water. Among ozonides of cyclic unsaturated compounds, those of six- and seven-membered rings are stable in comparison with those of five membered rings. Ozonides of very high molecular compounds, such as those of rubber, resinify when heated with water.

Alkalies destroy peroxides formed during ozonization and thus eliminate side reactions induced by these compounds. Furthermore, hydrolytic decomposition of ozonides takes place more readily in the presence of sodium hydroxide, although the use of alkalies is to be avoided if the aldehydes and ketones resulting from the decomposition are alkali-sensitive. Calcium carbonate has been employed successfully in connection with ozonides of unsaturated compounds obtained from the degradation of rubber.

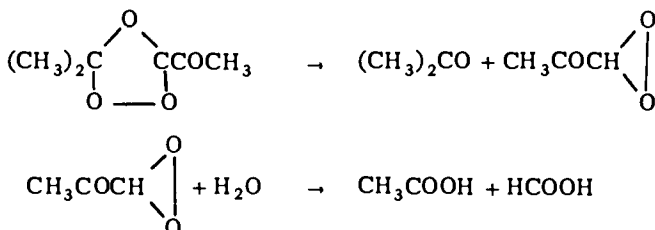
Ozonides of mesityl oxide, phorone, and ethylene are very easily decomposed by water. These compounds react with water with evolution of much heat, and many decompose explosively. A safe procedure is to dilute the vapors of the ozonide with an indifferent gas and to introduce the required quantity of water vapor into the mixture. Glyoxal may be obtained by this method from acetylene ozonide without difficulty.²⁹⁵

Ozonides of unsaturated keto and aldehyde chlorides are best decomposed by first drawing a stream of moist air through the solution of the ozonide, then completing the reaction by adding water and warming carefully.²⁹⁶

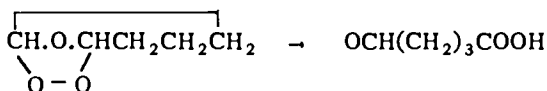
Sensitive ozonides are poured on ice, the resulting mixture of ice and ozonide solution is allowed to warm to room temperature, and the whole is finally warmed with care. Less sensitive ozonides may be decomposed by slowly heating their aqueous solutions to boiling. The more stable ozonides may require heating for a considerable period. It should be pointed out that the products of decomposition are often volatile, and when it becomes necessary to heat the ozonide solution for a long period, provision should be made for preventing loss of the products of decomposition.

In rare instances ozonization and the hydrolytic cleavage of the ozonide may be carried out simultaneously. This is possible, for example, with terpenes, ethereal oils, α -stibazole and allylamine.²⁹⁷

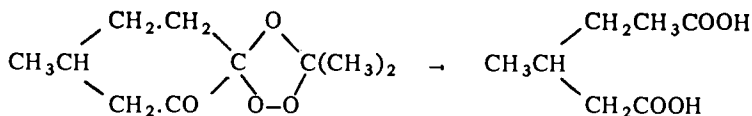
The hydrolytic decomposition of ozonides is occasionally accompanied by the formation of appreciable quantities of compounds resulting through oxidative changes of the intermediates formed. Thus, the ozonide of mesityl oxide, when decomposed with water, gives formic and acetic acids in addition to the expected methyl glyoxal, possibly through a breakdown of methylglyoxal peroxide formed as an intermediate, as follows:



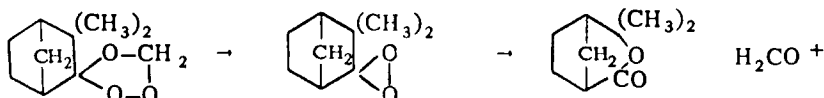
Cyclopentene ozonide is smoothly hydrolyzed by water, giving chiefly glutaric monoaldehyde:



A similar transformation is observed with pulegone ozonide, resulting in the formation of β -methyladipic acid:

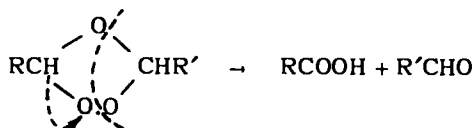


Camphene ozonide yields largely a lactone

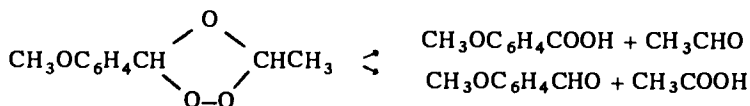


together with a small amount of camphenolone.

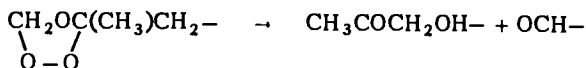
These examples illustrate the so-called *acid rearrangement*, which may be pictured as occurring in the following manner:



If R and R' are not identical, two different aldehydes and acids may form. Anethole ozonide, for example, gives chiefly anisic acid and acetaldehyde in the absence of water, but breaks down largely to anisaldehyde and acetic acid when heated with water.²⁹⁸



An abnormal transformation is observed with the ozonides of citronellal and citronellol, which gives rise to a keto alcohol probably in the following manner.²⁸⁷

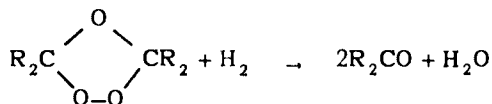


Other Methods of Decomposition

Ozonides may be decomposed by boiling with glacial acetic acid, alcohol and certain other solvents, the results being comparable with those obtained by hydrolytic cleavage. Peroxide formation takes place more readily in acetic acid, but a better yield of the aldehyde is obtained when decomposition is carried out in this solvent. The addition of formic acid improves the yield of aldehydes by inhibiting the oxidative processes.

Acids are formed as the products of cleavage when the decomposition of ozonides in a solvent is carried out in the presence of oxidizing agents, such as alkaline permanganate or hydrogen peroxide. Chromic acid in acetic acid solution is also effective in bringing about this reaction.

Cleavage of ozonides may be brought about by *reduction* with various agents.²⁹⁹ The reduction apparently proceeds in the following manner:



It is important to carry out the reduction immediately upon completion of the ozonization step in order to avoid the formation of products resulting from "acid rearrangement". Aluminum amalgam and water, potassium ferrocyanide, sodium hydrosulfide, sodium dithionite, sulfur dioxide, zinc dust and water containing some silver nitrate, hydroquinone, or dioxane have been employed for the purpose with some measure of success.³⁰⁰ Treatment with pyruvic acid has given good

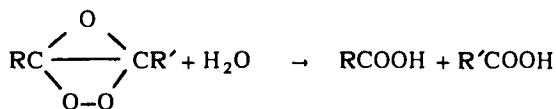
results with carbohydrates. Reduction proceeds readily in most instances with evolution of heat. Ozonides which yield particularly sensitive aldehydes or ketones may be reduced with good result by use of potassium ferrocyanide, since then, the formation of tarry product is largely avoided.³⁰¹ The more resistant ozonides may be reduced by heating with zinc dust and glacial acetic acid. Undesirable radical chain reactions are stopped at the end of the reaction by the addition of hydroquinone.

Catalytic hydrogenation is a highly satisfactory method for the reductive cleavage of ozonides.²⁹⁹

Reduction may be carried out by shaking the ice-cooled solution in a flask under an atmosphere of hydrogen with 0.5 gm of a catalyst containing 5% palladium supported on calcium carbonate. Usually 0.6 to 1 mole of hydrogen per mole of ozonide are consumed in the reduction, and yields range 50 to 90% of theoretical. The method works best when small amounts of the ozonides are treated.

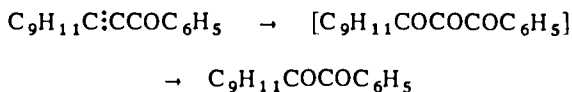
The reduction of polymeric ozonides cannot be carried out at ordinary temperature because of the low solubility of these substances. Reduction may be effected by heating in an autoclave under hydrogen pressure. Decomposition of the aldehydes formed may be prevented by using methanol or ethanol as solvents, when the compounds are obtained in the form of the stable acetals. Cyclohexene ozonide has been converted to succinaldehyde in 60% yield by this method.

The decomposition of ozonides of acetylenic compounds generally results in the formation of acids:



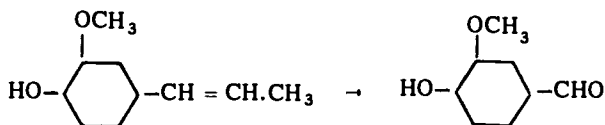
Acids are obtained in nearly quantitative yield from ozonides of stearolic and propiolic acids. It is possible, however, to obtain aldehydes from acetylenic ozonides by careful regulation of reaction conditions. Glyoxal has been obtained, in effect, in 81% yield by the careful decomposition of acetylene ozonide with water.³⁰²

Ozonization of benzoylmesitylacetylene results in the formation of mesityl phenyl diketone:³⁰³



Preparative Value of Ozonization of Unsaturated Compounds

The importance of ozonization of unsaturated compounds derives largely from its use for the determination of the position of multiple bonds. The method has found a limited application, however, for the preparation of certain carbonyl compounds. Vanillin and other phenolic aldehydes may be obtained through the ozonization of isoeugenol and other unsaturated aromatic compounds:³⁰⁴



Aldehyde esters, such as methyl *n*-aldehydeoctanoate $\text{OCH}(\text{CH}_2)_7\text{COOCH}_3$, methyl β -aldehydononanoate and methyl λ -aldehydododecanoate have been prepared from methyl oleate, methyl undecylenate and methyl erucate by ozonization and subsequent decomposition of the ozonide:³⁰⁵

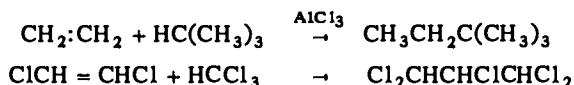


The ester aldehydes have been isolated by fractionation, in the pure form, boiling over a five degree range, in yields exceeding 55% of the theoretical.

The less stable dialdehydes, glutaraldehyde, adipaldehyde and pimaldehyde have been obtained in 50 to 75% yield by ozonization of cyclopentene, cyclohexene and cycloheptene, and subsequent decomposition of the ozonides obtained.

Application of Friedel-Crafts Method to Unsaturated Compounds

Unsaturated compounds react with various organic compounds in the presence of aluminum chloride to yield *addition* products. This is unlike the reaction of halogenated compounds with aromatic bodies, which involves the substitution of a hydrogen atom in the aromatic compound by the group combined with the halogen in the halo compound. The reaction takes place with hydrocarbons or with halo compounds, as illustrated by the following:



Aromatic hydrocarbons, such as benzene, show this ability to combine with unsaturated compounds, the reaction of the hydrocarbon with ethylene leading to the formation of ethylbenzene:



The reaction of olefins with aromatic compounds has also been found to be catalyzed by *boron trifluoride*. A second substituent apparently enters the *para* position, however, when this agent is used as a catalyst, whereas aluminum chloride causes the entrance of the substituent at the *meta* position.⁴¹⁴

Reaction of Olefins with Aliphatic Hydrocarbons

Aliphatic hydrocarbons may be alkylated by reaction with olefins or cycloolefins in the presence of anhydrous aluminum chloride.³⁰⁶ The reaction, which takes place under mild conditions, appears to be general. Both normal and iso paraffins react well when aluminum chloride activated with hydrogen chloride is used as a catalyst, only methane and ethane failing to react.³⁰⁷ Normal aliphatic

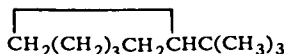
hydrocarbons from butane to decane have been alkylated by this method by reaction with ethylene, propylene and amylenes.

The procedure may be illustrated by that followed in the ethylation of normal hexane: Pure ethylene is passed through 147.7 gm of pure n-hexane to which small quantities of aluminum chloride are added from time to time, until a total of 25.1 gm have been introduced. A little dry hydrogen chloride is passed through the reaction mixture whenever a marked decrease in the rate of absorption of ethylene is observed. In one experiment, the amount of ethylene absorbed in the course of thirteen hours was 61.3 gm, the product separating as a colorless liquid, free from chlorinated compounds, and containing only traces of the catalyst. The yield was 75% of the theoretical.

An alternative procedure is illustrated by the ethylation of cyclohexene; 295 gm of the compound are heated to 50-60° on the water bath and saturated with hydrogen chloride and ethylene. Thirty grams of anhydrous aluminum chloride are added and ethylene is passed through the mixture for 13 hours at the rate of 4.5 liters per hour, gaseous hydrogen chloride being introduced into the mixture for periods of half-hour at hourly intervals. The liquid layer is then fractionated. The product boiling above 90°, amounting to 162 gm, consists of alkylated cyclohexane.

Polyalkylated products are often formed in addition to the monoalkylated product. The reaction is also often complicated through processes of isomerization, degradative autalkylation, polymerization of olefins and formation of complexes with the catalyst.

Cyclohexene reacts readily with paraffin hydrocarbons. The product first formed by reaction with tertiary butane is probably tertiary butylcyclohexane,



The final product isolated is dimethyl ethyl cyclohexane. Hydrogenation of some of the cyclohexene also takes place during the reaction, the hydrogen probably resulting from the coupling of the molecules of the alkylated cyclohexane, or other similar condensations.

Reaction of Olefins with Chlorinated Hydrocarbons

The reaction of chlorinated hydrocarbon with olefins in the presence of aluminum chloride may involve the combination of one halogen atom of the saturated halide with one of the unsaturated carbon atoms, while simultaneously the organic residue combines with the other unsaturated carbon atom:



Few olefins, and a restricted number of halogenated hydrocarbons, are capable of undergoing the reaction.³⁰⁸ Ethylene fails to undergo the reaction, but chlorinated ethylenes are capable of reacting. Of the latter, monochloroethylene reacts most readily and tetrachloroethylene least readily. Among the saturated halohydrocarbons mono and dichloromethanes do not react, but chloroform and carbon tetrachloride are capable of reaction. Some chloroethanes also react, although less readily than chloroform or carbon tetrachloride. It should be noted that chloroethanes are dehydrohalogenated and resinified under the influence of aluminum chloride.

2,2-Trichloroethane reacts with 1,2-dichloroethylene when a mixture of equal quantities of these compounds is treated with 1% of anhydrous aluminum chloride and the mass is warmed to 35-40° for five days. Crude 1,2,3,4,4-pentachlorobutane is obtained in this manner in 50% yield.³⁰⁹



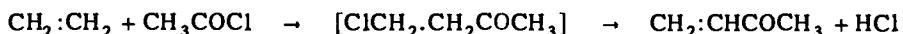
Sym-dichloroethylene, trichloroethylene and vinyl chloride react with 1,1-dichloroethane in the presence of aluminum chloride at 60° to form chlorobutanes.³¹⁰ Sym-dichloroethylene reacts readily with hexachloropropene at 5-6° in the presence of aluminum chloride to form the expected octachloropentene in good yield.³¹¹ Trichloroethylene reacting with hexachloropropene gives nonachloropentene in 82% yield together with a little dodecachloroheptene.³¹² The condensation of chloroform with dichloroethylene fails to proceed to completion owing to the formation of high boiling condensation products which combine with the catalyst.³¹³ Hexachloroethane and sym-tetrachloroethane do not react.

Among the chlorinated propanes only pentachloropropane is capable of condensing with reactive unsaturated bonds.

The presence of an unsaturated bond in a vicinal position activates the chlorine in a CCl_3 or CCl_2 group, so that condensation with reactive ethylenic bonds becomes possible. This rule does not hold with respect to an unsaturated bond in a ring.

Reaction of Olefins with Acid Chlorides

Olefins and cycloolefins react with acid halides in the presence of aluminum chloride to form, in general, unsaturated ketones, the acyl group replacing a hydrogen atom in the olefinic group $\text{C}=\text{CH}$.³¹⁴ Saturated chloro ketones are formed as intermediates in this reaction, a fact which has been established by isolating these compounds from the products, when reaction was carried out at a sufficiently low temperature:



Chloro ketones are obtained, for example, when the olefin, acid chloride and aluminum chloride are added simultaneously to carbon disulfide cooled to 0° or a lower temperature. Unsaturated ketones are also formed in this reaction in varying yields.³¹⁵ The saturated chloro ketone may be converted to the unsaturated ketone by heating.

The preparation of methyl trimethylethylene ketone may serve to illustrate the procedure: Equimolecular quantities of trimethylethylene and acetyl chloride, together with a half molecular equivalent of aluminum chloride are added to carbon disulfide cooled to 0°; the mixture is slowly heated to its boiling point and is boiled for about two hours.

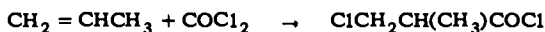
The yield of ketone is improved when the reaction mixture is cooled slowly, and the decomposition of the catalyst is effected by the addition of a mixture of ice and sodium carbonate. The yield of unsaturated ketone is generally about 20% of the theoretically expected.

Under similar conditions, a 30% yield of the unsaturated ketone is obtained with hexene-2, and a 40% yield with heptene-3 and octene. A 71% yield of the olefinic ketone is obtained with *n*-propylene. The reaction of acetyl chloride with ethylene does not proceed smoothly.

β -Chloropropiophenone has been obtained in 87-92% yield by the reaction of benzoyl chloride with ethylene in the presence of aluminum chloride, by using ethyl bromide as a solvent and introducing the ethylene into the liquid under slight pressure.³¹⁶ β -Halo ethyl alkyl ketones have also been prepared through the reaction of aliphatic acyl chlorides with ethylene in the presence of aluminum chloride, di-(β -chloroethyl) ketone being obtained, for example with β -chloropropionyl chloride.³¹⁷

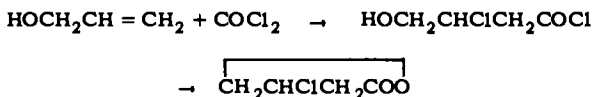
Halogenated unsaturated ketones may be secured through the reaction of acid halides with vinyl halides in carbon tetrachloride, in the presence of aluminum chloride at ordinary temperature and pressure.³¹⁸ Chlorovinyl methyl ketone has been obtained in this manner by the reaction of acetyl chloride with vinyl chloride, and isobutyl β -chlorovinyl ketone from isovaleryl chloride and vinyl chloride. As in other similar reactions, the saturated chloro ketones are first formed, but are readily dehydrohalogenated to the unsaturated ketones.

β -Chloro acid chlorines are obtained through the reaction of olefins with phosgene in the presence of aluminum chloride:⁴⁹³

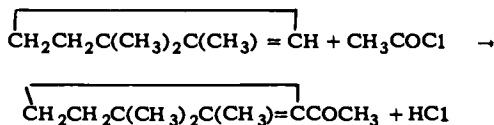


Esters of the halo acids may be obtained by treating the chloride with alcohol. Methyl β -chloropropionate has been obtained in this manner by conducting ethylene through a solution of phosgene in carbon disulfide containing aluminum chloride, and heating the solution of the resulting crude chloride with methanol at 0°.³¹⁸

The reaction of phosgene with unsaturated alcohols leads to the formation of chloro-lactones:



The interaction of 1,1,2-trimethyl-2-cyclopentene with acyl halides in the presence of aluminum chloride leads to the formation of the acylated hydrocarbon:³¹⁹



Methyl 1-chlorocyclohexyl ketone has been prepared from cyclohexene and acetyl chloride; treated with dimethylaniline, the chloro ketone is converted to the unsaturated ketone.³²⁰ The transformation may also be brought about by heating. Methyl cyclohexenyl ketone has been obtained by this procedure in 60% yield. The corresponding phenyl derivative prepared from cyclohexene and benzoyl chloride has been obtained in lower yield. There is danger of much polymerization if the conversion to the unsaturated ketone is effected directly, without preparation, first, of the saturated chloro ketone.

Some benzoylcyclohexane has been obtained on carrying out the condensation of cyclohexene with benzoyl chloride in the presence of cyclohexane, apparently through the reduction of the chloroketone by nascent hydrogen. The latter was probably formed through the condensation of two molecules of cyclohexane to dicyclohexane in the presence of aluminum chloride.

Acyl halides also react with acetylenic compounds in the presence of aluminum chloride. β -Chloroethylene ketones are obtained as the product of the reaction of acetylene with acid chlorides:



The reaction has been carried out with various homologs of acetylene and with acetyl, propionyl, butyryl, isovaleroyl, stearoyl and benzoyl chlorides.

n-Butane and higher aliphatic hydrocarbons react with acetyl chloride in the presence of aluminum chloride to form methyl ketones. Reaction with n-butane proceeds at 50 to 60°. Reaction seems to involve a reversible isomerization of the hydrocarbon, dehydrogenation, addition of the acetyl chloride at the resulting olefinic bond, and finally loss of the elements of hydrogen chloride.⁵²⁰

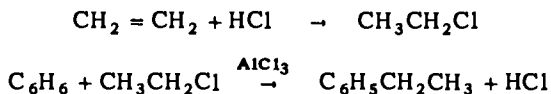
Addition of acetyl chloride at the ethylenic bond of cyclohexene takes place in the presence of aluminum chloride; loss of the elements of hydrogen chloride follows with the formation of cyclohexyl methyl ketone.⁵²¹

Reaction of Olefins with Aromatic Compounds

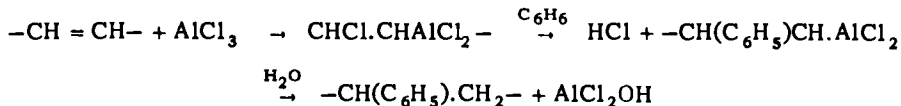
Reaction with Aromatic Hydrocarbons

The reaction of aromatic hydrocarbons with olefins in the presence of aluminum chloride leading to the formation of alkylated aromatic compounds appears to be of general applicability. Benzene homologs, polynuclear hydrocarbons, phenols and phenol ethers all react more readily than benzene.³²¹

The addition of olefins to aromatic compounds has been assumed by some to proceed through the formation of a saturated halo compound resulting from the interaction of the olefin with hydrogen halide.³²² The latter is presumably formed by the action of the small amount of water present in the reaction mixture on aluminum chloride, and is continually regenerated as the reaction between the halo and the aromatic compounds proceeds. Considering, as an example, the reaction of ethylene with benzene, the successive steps in the reaction would be as follows:



Olefins are known to form complexes with aluminum chloride,³²³ and it is possible that these addition products play a part in the reaction of aromatic compounds with olefins, and an alternative mechanism of the reaction may be formulated as follows:



It is possible that the reaction follows both courses.

The procedure employed in carrying out the ethylation of aromatic hydrocarbons is to pass ethylene through a mixture of the hydrocarbon with aluminum chloride heated to 70-90°, the mixture being vigorously agitated during the passage of the gas.³²⁴ For the ethylation of benzene one molecular equivalent of aluminum chloride to thirteen of benzene appears to be the best proportion. A good procedure is to saturate the benzene-aluminum chloride mixture with hydrogen chloride prior to the passage of ethylene at

atmospheric pressure. The optimum temperature for the ethylation of benzene appears to be somewhat below 75°.

The reaction of olefins with aromatic compounds proceeds further, after the formation of the monoalkylated product, and di and polyalkylated compounds are also formed.

In the reaction of benzene with ethylene by the procedure described above, in addition to ethylbenzene, which is obtained in 30% yield, there are formed di and triethylbenzenes, the total yield of these compounds amounting to a little less than 20% of theoretical. The *meta* isomer forms the major part of the diethylbenzenes formed.³²⁵ Tetra-, penta- and hexaethylbenzenes are also found in the reaction product in smaller quantities.

Hexaethylbenzene may be obtained in over 90% yield when approximately 5.7 molar proportion of ethylene is passed through the liquid. Fairly high yields of hexaethylbenzene may be obtained by carrying out the reaction under pressure.³²⁶

Propylene reacts much less readily than ethylene with benzene and other aromatic compounds.

In the alkylation of benzene with olefins derived from kerosene or gasolenes by cracking, the use of 0.1 molar fraction of aluminum chloride to one molecular equivalent of the olefin in 9 to 10 molar equivalents of benzene appear to be the best proportions. The optimum reaction temperature is in the range 25 to 30°. A satisfactory procedure is to add the olefin gradually to the mixture of benzene and the catalyst. There is an induction period when aluminum chloride is used, but the reaction proceeds forthwith when aluminum bromide is used as a catalyst. The tar-like layer formed in the reaction with aluminum chloride is an effective catalyst of the reaction. The yields of alkylated benzenes resulting by this method are generally in the neighborhood of 60%, and may reach 76% of the theoretical.³²⁷

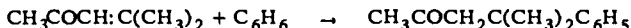
In the reaction of higher olefins with benzene in the presence of aluminum chloride, cleavage of the olefin may precede alkylation; thus, benzene reacting with diisobutylene gives *tert*-butylbenzene and di-*tert*-butylbenzene following cleavage of the diisobutylene.³²⁸

The phenyl group may displace aromatic groups attached to the ethylenic group; replacement of aromatic groups with hydrogen and reduction of the unsaturated linkage may take place simultaneously. Bibenzyl results for example, on attempting to condense 1,1-bis-(*p*-chlorophenyl)-2-phenylethylene with benzene in the presence of aluminum chloride.³²⁹ Bibenzyl results also, under similar conditions, from *sym*-tetraphenylethane and from tolan.

The reaction is applicable to *unsaturated ketones*; their behavior is indicated by the following examples:

Ketene reacting with aromatic hydrocarbons in the presence of aluminum chloride gives aryl methyl ketones.³³⁰ The yields of ketone are generally low, acetophenone being obtained from ketene and benzene in 32 to 37% yield.

Mesityl oxide reacting with a large excess of benzene at 0°, in the presence of 1½ molal equivalent of aluminum chloride gives β -phenylisobutyl methyl ketone:³³¹



The ketone is obtained in 80% yield when mesityl oxide is added gradually, in the course of one hour, to the well-agitated mixture of benzene and aluminum chloride, and stirring is continued for three hours.

Benzalacetophenone gives β,β -diphenylpropiophenone in good yield under similar

conditions.³³² Benzalmenthone also gives the corresponding ketone readily, but anisalacetophenone fails to react.³²⁹ It is of interest to note that the latter forms a very unstable hydrochloride.

The reaction of aromatic compounds with unsaturated carbonyl compounds in which the double bond is conjugated with the carbonyl bonds is reversible. Hydrogenation and replacement of aromatic groups has also been observed with this type of compounds, the hydrogen resulting through the coupling of hydrocarbons. Benzalacetone and its p-methyl or p-chloro derivatives are, thus, partially converted to benzhydrylacetone when treated with a benzene suspension of aluminum chloride.

The reaction of *unsaturated acids* with aromatic compounds often results in the formation of oily products, a fact which has been responsible for the prevalence of a great deal of confusion regarding the nature of the products of reaction. Little is known, in many cases, about the position of the entering group. Resinous products are also obtained as a by-product, apparently as a result of the polymerizing effect of aluminum chloride upon the unsaturated compound.³³³ The normal addition is known to proceed however, and yields of the arylated acid increase with increase in the distance of the multiple bond from the carboxyl group.³³⁴ It may be noted that the iodine number of unsaturated acids approaches the theoretical as the distance of the double bond from the carboxyl group increases.³³⁵

Unsaturated acids which do not react with methyl iodide in the Hübl solution, (*) do not react with benzene.

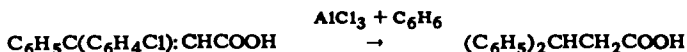
The position of the phenyl group in the product of the reaction of benzene with some unsaturated compounds has been determined.³³⁷ Crotonic acid has been shown to yield β -phenylbutyric acid; Δ -isopentenic acid, $(\text{CH}_3)_2\text{C}=\text{CHCOOH}$, is found to form phenylisopropylacetic acid, $(\text{CH}_3)_2\text{CHCH}(\text{C}_6\text{H}_5)\text{COOH}$. α,β -Dimethyl- β -phenylpropionic acid, $\text{CH}_3\text{CH}(\text{C}_6\text{H}_5)\text{CH}(\text{CH}_3)\text{COOH}$ is obtained from tiglic acid, $\text{CH}_3\text{CH}=\text{CH}(\text{CH}_3)\text{COOH}$; β,β -diphenylpropionic acid from cinnamic acid; α -methyl- β,β -diphenylpropionic acid from α -methyl cinnamic acid; α -ethyl- β,β -diphenylpropionic acid from α -ethylcinnamic acid; α,β,β -triphenylpropionic from α -phenylcinnamic acid. Phenylisocrotonic acid yields γ,γ -diphenylbutyric acid; allylacetic acid gives γ -phenylvaleric acid; β,γ -hydrosorbinic acid, $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{COOH}$, yields phenylhexyl acid.

n-Crotonic and phenylacrylic acids do not react with benzene in the presence of aluminum chloride, and in the reaction of other α,β -unsaturated acids with benzene, the phenyl group does not generally add at the point where the unsaturated bonds were originally situated.³³⁸ Thus, 2-hexenoic acid yields 5-phenylcaproic acid, and 3-methyl-2-hexenoic acid yields 3-methyl-5-phenylcaproic acid exclusively. It should be noted that 2-hexenoic acid in solution in carbon disulfide is converted to 3- or 4-hexenoic acid under the action of aluminum chloride.

(*)The Hübl solution consists of a mixture of 25 gm iodine in 500 cc of 90% alcohol and 30 gm of mercuric chloride in 500 cc 90% alcohol. The solution is kept for 48 hours before use.³³⁶

β,β -Diphenylpropionic acid results through the reaction of *o*- and *p*-chlorocinnamic acids with benzene in the presence of aluminum chloride, and β,β -bis-(*p*-chlorophenyl)-propionic acid results through the reaction of these same acids with chlorobenzene.³³⁹ The normal addition product is probably formed first, then the chlorophenyl group is apparently replaced by a phenyl or a new halophenyl group.

Hydrogenation as well as substitution of an aryl group takes place in the reaction of β -(*p*-chlorophenyl)-cinnamic acid with benzene:³⁴⁰

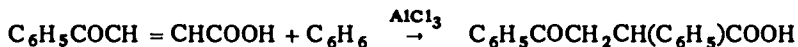


The reaction of *oleic acid*³⁴¹ with an excess of benzene proceeds rapidly in the presence of an approximately equimolecular quantity of aluminum chloride, and is complete within less than five minutes. The products formed are 9- and 10-phenyloctadecanoic acids in approximately equal quantities.³⁴² Products with lower neutralization equivalent are formed when the aluminum chloride is in considerable excess, and the mixture is subjected to prolonged boiling. Very little condensation takes place with less than one third equivalent of aluminum chloride.³⁴¹

Good yields of arylated stearic acids are obtained also with other aromatic hydrocarbons and their derivatives.³⁴³ The reaction may be effected by adding 0.75 mole of aluminum chloride, in portions, to a cold solution of 0.709 mole *oleic acid* in an excess of the aromatic compounds, raising the temperature slowly to 80° and continuing to heat for six hours.

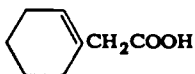
Elaidic acid and other unsaturated acids also react readily with aromatic compounds under appropriate conditions. The reaction would appear to be of general applicability, homologs of benzene, naphthalene, anthracene, nitrobenzene, anisole, phenetole, etc., adding readily to unsaturated acids capable of reaction with benzene.

Unsaturated *keto acids* add benzene or toluene at the double bond:³⁴⁴



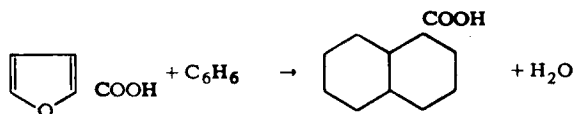
The use of a large excess of the catalyst and of the aromatic hydrocarbon is required, and the yield of the addition product is low.

In the reaction of Δ^1 -cyclohexenylacetic acid,



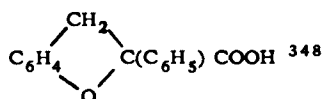
with benzene in the presence of aluminum chloride, migration of the phenyl group to the 4-position occurs.³⁴⁵

Furoic acid reacting with benzene in the presence of aluminum chloride gives α -naphthoic acid:³⁴⁶



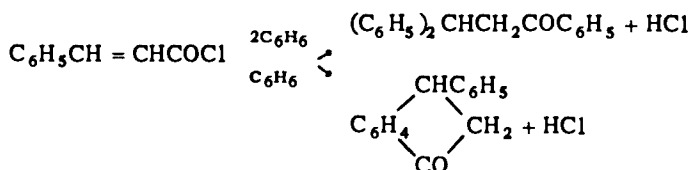
An analogous reaction takes place also with chlorobenzene, toluene and anisole, giving 6-substituted 1-naphthoic acids.³⁴⁷ Methyl furoate reacts in a similar manner, while methyl 2-Methyl-3-furoate gives with benzene, methyl 4-phenyl-4,5-dihydro-2-methyl-furoate.³⁴⁷

Coumaric acid gives with benzene, α -phenyl- α,β -dihydrocoumarilic acid,

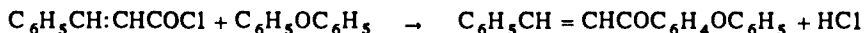


Esters of unsaturated acids react with benzene and its derivatives in the same manner as the free acids. As with the latter, the yield of the addition compound increases with increase in the distance of the unsaturated bond from the carboxylic group. Derivatives of benzene containing para directing substituents give better yields than benzene.³⁴⁹

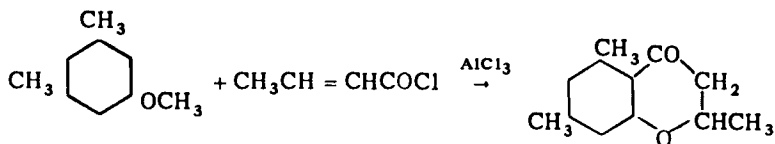
The reaction of *unsaturated acid chlorides* with aromatic hydrocarbons in the presence of aluminum chloride is complicated by the fact that both the acyl chloride group and the unsaturated bonds are capable of reaction. Cinnamoyl chloride and benzene give an open-chain and a cyclic saturated ketone:³⁵⁰



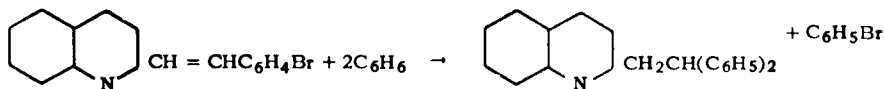
A mixture of β,β -diphenylpropionic acid and β,β -diphenylpropiophenone are obtained when the reaction is carried out with an excess of benzene.³⁵¹ Addition at the double bond takes place with other hydrocarbons, but only replacement of the acyl halogen occurs with diphenyl ether:³⁵⁰



The reaction of crotyl chloride and β,β -dimethylacrylyl chloride results only in the replacement of the chlorine atom with an aromatic group, 3,5-xylenol methyl ether forming an exception and giving a chromanone with both acids, crotyl chloride giving a trimethyl derivative:³⁵²



In the reaction of halo benzenequinolindines with benzene in the presence of aluminum chloride the halogen-free α -benzhydrylquinolindine is formed:³⁵³



A similar replacement of the substituted phenyl groups has been observed with *p*-chloro- and *p*-methylbenzalacetone and other similar compounds.³⁵⁴

The reaction of cyclopentene with benzene results in the formation, principally, of cyclopentylbenzene.³⁵⁵ *Cyclohexyl* reacts vigorously with benzene in the presence of aluminum chloride forming cyclohexylbenzene and higher boiling products;³⁵⁶ reaction with toluene may be so conducted as to give a 33% yield of cyclohexyltoluene.³⁵⁷ *p*-Xylene gives a 45% yield of 2-cyclohexyl-1,4-dimethylbenzene; *m*-xylene an 81% yield of the 5-cyclohexyl-1,3-dimethyl derivative; mesitylene 35% of the 2-cyclohexyl-1,3,5-trimethyl, and cymene 40% of the cyclohexyl-1-isopropyl derivative.

Naphthalene does not react with ethylene at 100-200° in the presence of aluminum chloride. The reaction of polynuclear hydrocarbons in general with ethylene proceeds with greater difficulty than with the higher olefins. Reaction with ethylene may be brought about at temperatures in excess of 100° under pressure.

Reaction of Olefins with Phenols

Phenols and naphthols react readily with unsaturated compounds in the presence of aluminum chloride. The reaction is quite general and proceeds most readily with olefins with three or more carbon atoms. The reaction may be initiated, if necessary, by the addition of small amounts of an alkyl halide or a hydrogen halide. Carbon tetrachloride may be used as a solvent.³⁵⁸

p-*tert*-Butylphenol is obtained in 77.8% yield when a mixture of 56 gm of *tert*-isobutylene, 94 gm of phenol, 9 gm of *tert*-butyl chloride and 5 gm of aluminum chloride is heated at 100° under 5 atm pressure for two minutes.

The product obtained from the reaction of diisobutylene with phenol depends upon the reaction conditions. *tert*-Butylphenol results in 67% yield when 1 and 1/3 moles of aluminum chloride are added gradually to a mole of phenol, while 1/2 mole of diisobutylene is added slowly, heating the mixture gradually during the addition, and the mass is finally heated on the steam bath for 6 hours. More vigorous conditions lead to the formation of increasing amounts of *tert*-butylphenol, whereas milder conditions tend to produce tetramethylbutylphenol.³⁵⁹

Ring closure takes place when phenols are condensed with 1,5-diolefins in the presence of aluminum chloride. Thus, phenol and 2,5-dimethyl-1,5-hexadiene gives 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthol, with a smaller amount of a chromane derivative formed through the reaction of the first product with an additional molecule of the diolefin.³⁶⁰

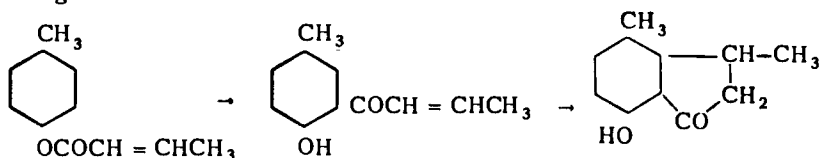
Alkylation of *phenol ethers* proceeds well by reaction of these compounds with olefins in the presence of aluminum chloride. *m*-Cresol methyl ether, for example, reacting with isobutylene, gives *o*-butyl-1-*m*-cresol methyl ether in 58% yield,³⁶¹ and 3-*tert*-butyl-*p*-cresol methyl ether results in 61% yield from *p*-cresol methyl ether and the same olefin. 4-*tert*-Butylresorcinol dimethyl ether is similarly obtained in 71% yield from resorcinol dimethyl ether and isobutylene.³⁶²

Ring closure takes place by the reaction of 1,5-diolefins with phenol ethers as with phenols.

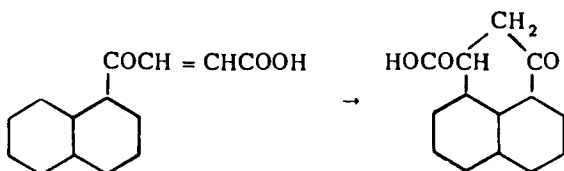
Cyclization through Intramolecular Condensations Involving Unsaturated Bonds

The condensation of an aromatic nucleus in the presence of aluminum chloride with the unsaturated bonds of a group attached to the nucleus results in ring

closure. The unsaturated bonds may be present in an open chain group, or in a ring. Examples of the former type are offered by the formation of 3,4-dimethyl-7-hydroxyhydrindone from *p*-cresyl crotonate, after the latter undergoes a Fries rearrangement:³⁶³

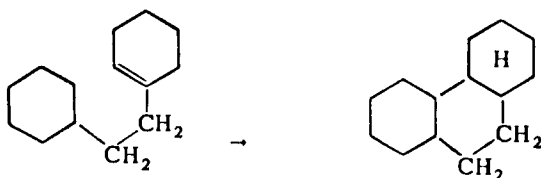


and the formation of a dihydronaphthindone carboxylic acid from β -1-naphthoxyacrylic acid:³⁶⁴

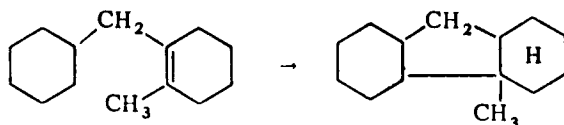


1-Cinnamyl-naphthalene also undergoes a similar cyclization.³⁶⁵ It should be noted that in these examples an activated hydrogen of the aromatic nucleus is involved in the condensation process.

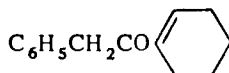
Many cyclizations have been carried out involving an unsaturated bond in a ring. 1- β -Phenylethyl- Δ^1 -cyclohexene undergoes ring closure under the influence of aluminum chloride to form octahydrophenanthrene:³⁶⁶



1-Benzyl-2-methylcyclohexene yields a methylhydrofluorene:³⁶⁷

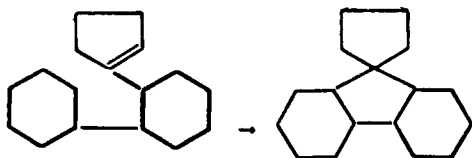


Substituted benzal-2-methylcyclohexenes also undergo ring closure, but benzylcyclohexene gives only polymerization products. Phenylacetylcyclohexene,

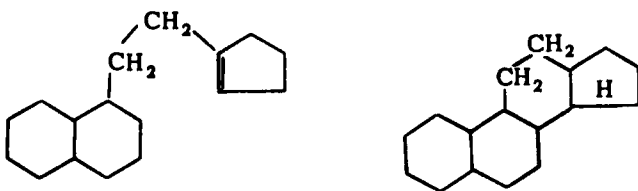


also fails to give a cyclic product.³⁶⁸

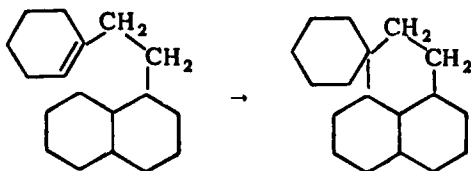
A spiran is obtained from 1-(*o*-biphenyl)- Δ^1 -cyclopentene:³⁶⁹



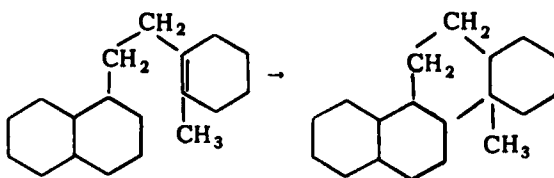
Cyclization takes place under mild conditions with 1-(β -1'-naphthylethyl)- Δ^1 -cyclopentene, which is converted to 1,2-cyclopentano-2,3,4-tetrahydrophenanthrene:³⁷⁰



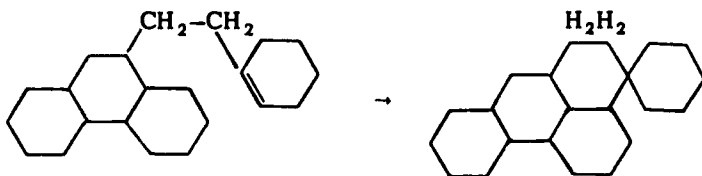
1-(α -Naphthylethyl)- Δ' -cyclohexene gives a spiro compound:³⁷¹



2-Methyl-(β -1'-naphthylethyl)- Δ' -cyclohexene is also capable of cyclization:



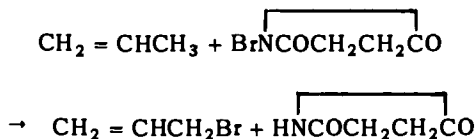
9-Phenanthrylethyl- Δ' -cyclohexene yields a spiran:³⁷²



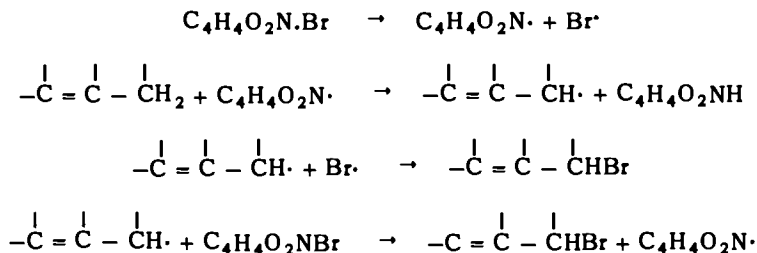
Wohl-Ziegler Reaction

The unsaturated group $\begin{array}{c} | \\ -C = C- \\ | \end{array}$ causes the activation of a methyl or methylene group to which it is attached. This is evident in the ready replacement of

a hydrogen atom in a group thus activated with bromine by reaction with N-bromosuccinimide and certain other N-bromoimides.³⁷³ This method of replacement of a hydrogen atom with bromine is known as the Wohl-Ziegler reaction. The halogen enters the so-called *allylic position* in the olefinic body:



The formation of an intermediate complex between the olefin and the bromide has been suggested,³⁷⁴ and a mechanism involving free radicals has been postulated as follows:³⁷⁵



Exchange takes place more readily with a methylene group than with a methyl group, while a tertiary hydrogen atom is generally unreactive. The method appears to be of general applicability.

N-Bromosuccinimide is the most satisfactory bromine exchanging reagent, although N-bromophthalimide may be employed with good results. N-Bromoglutaramide and N-bromohexahydrophthalimide are not satisfactory for the purpose.

The *procedure* adopted in carrying out the reaction is as follows: The olefin to be brominated is dissolved in carbon tetrachloride or other suitable solvent, the required quantity of N-bromosuccinimide is added and the mixture is heated under a reflux condenser. The end of the reaction is indicated by the disappearance of the insoluble N-bromimide from the bottom of the flask, or by a negative test with starch iodide paper, indicating the absence of active bromine. The succinimide formed floats to the surface of the liquid and is filtered off, the product being then isolated from the liquid by a suitable method.

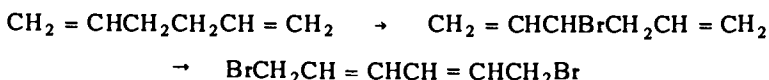
Carbon tetrachloride is the most generally used solvent, but benzene can be used to advantage in many cases, and chloroform has given satisfactory results, especially in large scale preparations. In many instances the reaction can be carried out in an excess of the olefins, without the use of a solvent.

The use of an excess of the olefin is often an advantage in many cases, as for example, in the bromination of aromatic hydrocarbons, phenols and related compounds. When sterols are brominated by this method, it is desirable to use the bromide in an equivalent quantity or in excess. The bromination of α, β -unsaturated steroids is best carried out in the dark, using an excess of bromosuccinimide and allowing the reaction to proceed for a longer period.

The reaction is usually carried out at the boiling temperature of the solution. In brominating the more reactive olefins, the reaction temperature may be lowered by using a low boiling solvent such as ether, or by the application of external cooling. Occasionally it may be desirable to carry out the reaction at a comparatively high temperature. Thus, while the complete bromination of 1-phenyl-1-propene at the refluxing temperature in carbon tetrachloride solution takes place in 15 hours, the reaction is complete almost instantaneously at 140°. Reaction at higher temperatures is generally carried out in the absence of a solvent. Bromination with *N*-bromoacetamide should be carried out at room temperature or in an ice-bath, even though reaction proceeds at a slow rate at these temperatures.

N-Bromosuccinimide may be prepared by quickly brominating succinimide in ice-cold alkaline solution. The compound is obtained in 78 to 81% yield.³⁷⁶ It is purified by rapidly crystallizing from hot water. The purity of the compound is determined iodometrically; it should analyze at least 97% bromoimide. *N*-Bromosuccinimide is stable for months in the absence of light and moisture.

The Wohl-Ziegler reaction is capable of catalytic acceleration, and the use of catalysts has extended the scope of the reaction. Dibenzoyl peroxide, used at the rate of 0.5-0.1 mole per mole of the bromide, is an effective catalyst,³⁷⁷ and diallyl has been successfully brominated in the presence of this compound:³⁷⁸



The dibromo compound is formed following an allylic rearrangement. Rearrangements of this type occasionally occur in the course of the Wohl-Ziegler reaction.

Nuclear bromination of aromatic compounds may be successfully effected with *N*-bromosuccinimide by use of a molecular proportion of chlorides of aluminum, zinc, or iron; sulfuric acid may also be employed for the purpose. Actinic rays also accelerate the reaction.³⁷⁹

In many instances the olefinic bromo compound formed in the Wohl-Ziegler reaction loses the elements of hydrogen bromide when the reaction mixture is subjected to prolonged refluxing. The bromo compound may be completely dehydrobrominated by means of a basic substance such as potassium- or sodium acetate, sodium carbonate, dimethylaniline, pyridine, collidine, alumina, etc.

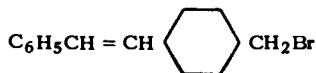
As examples of the application of the reaction to open chain olefinic compounds may be cited the formation of methyl γ -bromocrotonate from methyl crotonate,³⁸⁰ methyl γ -bromosenecioate from methyl senecioate. Methyl sorbate can be converted to methyl ϵ -bromosorbate $\text{BrCH}_2\text{CH} = \text{CHCH} = \text{CHCOOCH}_3$ by use of a catalyst, or by carrying out

the reaction at a higher temperature. The lactone $(\text{CH}_3)_2\text{C}:\text{CC}(\text{OCH}_3):\text{CHCOO}$ may be converted to the ϵ -bromo derivative, $\text{BrCH}_2\text{C}(\text{CH}_3):\text{CC}(\text{OCH}_3):\text{CHCOO}$,³⁸¹ and the lat-

ter to penicillic acid, $\text{CH}_2:\text{C}(\text{CH}_3)\text{C}(\text{OH})\text{C}(\text{OCH}_3):\text{CHCOO}$.

The reaction is applicable to many types of cyclic compounds, the essential condition, again, being the presence in the molecule of a methyl or methylene group attached to a carbon atom with a double bond.

The bromination of hydroaromatic hydrocarbons proceeds in a satisfactory manner at refluxing temperature in carbon tetrachloride solution, using the calculated amount of *N*-bromosuccinimide. Dehydrobromination of the product obtained from tetralin gives naphthalene in 74% yield, and of the product from *Sym*-octahydrophenanthrene gives phenanthrene in 63% yield. Styrylbenzyl bromide,



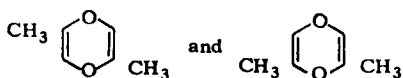
has been obtained from *p*-methylstilbene.³⁸² Toluene gives benzyl bromide in 64% yield when the reaction is carried out in the presence of peroxide. Derivatives of toluene containing electronegative substituents react in the absence of a catalyst. *Steroid dienes* $\text{RC}(\text{CH}_3)=\text{CHCH}=\text{C}(\text{C}_6\text{H}_5)_2$ may be brominated to



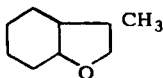
and the latter may be converted to compounds of the type $\text{RCOCH}_2\text{OCOCH}_3$, by reaction with potassium acetate, followed by oxidation.

Homologs of naphthalene, coumarin, pyrone, thiophene and furan may be brominated by the Wohl-Ziegler method. Bromination proceeds with increasing readiness with diminishing "aromaticity" of the compounds, although the stability of the products obtained decreases with increase in ease of their formation.³⁸³ 1-Methylnaphthalene and 2-methylnaphthalene are brominated in the side chain when the reaction is carried out in the absence of a catalyst. Ethers of α - and β -naphthol are brominated rapidly.³⁸⁴ Acenaphthene and anthracene are brominated in the 5- and 9-position. Higher polycyclic hydrocarbons, such as pyrene and chrysene, are readily monobrominated with *N*-bromosuccinimide.³⁸⁵

One methyl group in 2,5- and 2,6-dimethyl- γ -pyrone



may be brominated selectively. In contrast to a 3-methyl or 3-ethyl group, the 4-methyl group in coumarin is never attacked. 3-Methylbenzofuran,

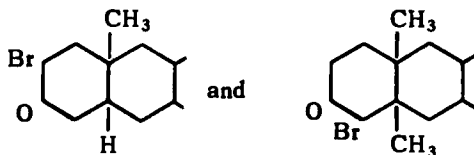


treated with a molecular equivalent of *N*-bromosuccinimide in the presence of benzoyl peroxide, gives the 2-bromo derivative, while with two molecular equivalents of the bromide it gives 2-bromo-3-(bromomethyl)-benzofuran.

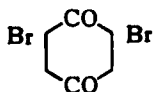
The methyl group in methylimidazolones³⁸⁶ and in methylthiophene can be readily brominated. 2-Bromomethyl-5-methylthiophene undergoes rearrangement when treated with a metallic cyanide to 3-bromo-2,5-dimethylthiophene.³⁸⁷ 3-Bromomethylthiophene also undergoes a similar rearrangement giving 2-bromo-3-methylthiophene.³⁸⁷

Activation of methylene groups may be brought about by a multiple bond between carbon and another element. It may be brought about, for example, by the double bond between carbon and oxygen in a carbonyl group. The Wohl-Ziegler method is therefore applicable to carbonyl compounds. Thus, cyclo-

hexanone and certain ketopelargonic acid derivatives readily yield α -bromo derivatives on treatment with bromosuccinimide.³⁸⁸ Saturated 3-keto steroids of the alio and normal series react rapidly with N-bromosuccinimide under strong illumination to form the 2-bromo and 4-bromo derivatives



Free hydroxyl and carbomethoxy groups do not interfere in the reaction. Tetrahydro- γ -pyrone gives the 5-bromo derivative³⁸⁹



In general in α,β -unsaturated ketones having methylene groups in α -position with respect to the carbonyl group and the double bond, the methylene group in the α -position with respect to the double bond is preferentially brominated.

Aldehydes may, apparently, be brominated by bromosuccinimide if the reaction is carried out at a sufficiently low temperature. This is borne out by the fact that cyclocitral, reacting with the bromoimide, gives a brominated product from which an aldehyde isomeric with safrole has been obtained by dehydrobromination.³⁹⁰

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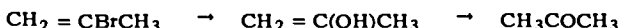
CHAPTER 18

UNSATURATED COMPOUNDS WITH FUNCTIONAL GROUPS

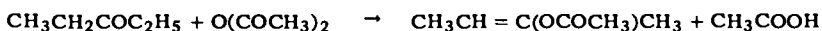
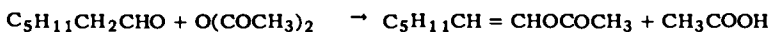
Unsaturated Alcohols

Unsaturated alcohols may be prepared by the general methods employed for the preparation of alcohols. They may be prepared, for example, by the replacement of halogen atoms in unsaturated halides with hydroxyl groups, the reduction of unsaturated aldehydes or ketones under mild conditions, and the reaction of Grignard reagents with unsaturated carbonyl compounds and subsequent hydrolysis of the resulting halomagnesium compound.

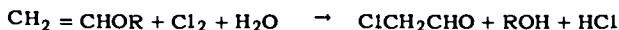
It should be noted that where, as a result of the normal course of a reaction, the formation of an unsaturated alcohol is expected, in which a hydroxyl group is attached to an unsaturated carbon atom, a saturated aldehyde or a ketone is obtained instead because of the inherent instability of the group $\text{>C}=\text{COH}$ — (Erlenmeyers rule¹).



Ethers and esters of alcohols of the type $\text{RR}'\text{C}=\text{C(OH)R}''$ are stable, however, and it is possible to prepare esters of the homologs of vinyl alcohol by heating aldehydes or ketones with acetic anhydride and sodium acetate:²



Vinyl ethers, treated with chlorine in the presence of water are decomposed to chloroacetaldehyde and an alcohol:



They react readily with alcohols and phenols to form acetals:¹⁴²



Sodium β -allyl alcoholate, $\text{CH}_2 = \text{C(ONa)CH}_3$, is apparently formed on heating acetone in dilute ethereal solution with metallic sodium.

Allyl carbinol, $\text{CH}_2 = \text{CHCH}_2\text{CH}_2\text{OH}$, is obtained through the reaction of allylmagnesium bromide with trioxymethylene, followed by hydrolysis of the magnesium compound formed.³ α -Methylallyl alcohol, $\text{CH}_2 = \text{CHCH(OH)CH}_3$, results as its halomagnesium derivative from the reaction of methylmagnesium iodide with acrolein.⁴

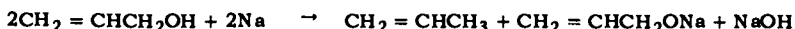
Unsaturated alcohols may be prepared by the reduction of unsaturated esters with sodium and alcohol. The method is not applicable, however, to α,β -unsaturated esters since the double bond in these compounds is attacked, and a saturated alcohol is obtained when they are reduced with sodium and alcohol.⁵

Unsaturated alcohols may be obtained also by exhaustive methylation of oxalkylamines and pyrolysis of the resulting quaternary oxalkylammonium bases.⁶

Higher olefinic alcohols may be successfully prepared by the reaction of higher olefinic aldehydes or ketones with organomagnesium compounds;⁷ also, through the reaction of higher saturated aldehydes or ketones with zinc and allyl iodide,⁸ or with magnesium and unsaturated halides.⁹ The Grignard reagent obtained from the unsaturated halides may be employed in this reaction instead of metallic magnesium and the halide.¹⁰ Higher olefinic alcohols may also be prepared through the selective reduction of higher unsaturated aldehydes¹¹ or ketones.¹²

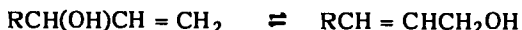
Alcohols with two allyl groups in their molecule may be prepared through the reaction of allyl iodide and zinc with fatty acid esters. Formic acid gives diallyl carbinol, $(\text{CH}_2 = \text{CHCH}_2)_2\text{CHOH}$, by this reaction, while other acids give tertiary alcohols.¹³ Alcohols with three allyl groups in the molecule have been obtained by the reaction of zinc and allyl iodide with halo fatty acid esters.¹⁴

Unsaturated alcohols reacting with sodium amide yield the corresponding alkylene, together with the unsaturated sodium alcoholate.¹⁵ Thus, propylene is formed when allyl alcohol is added dropwise to a solution of sodium amide in liquid ammonia at -40° :



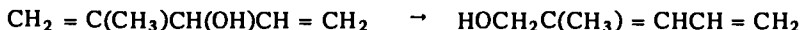
Allyl alcohol is not easily attacked by nascent hydrogen, although it can be reduced to normal propyl alcohol by boiling with zinc and sulfuric acid, potassium hydroxide and metallic aluminum, etc. This alcohol forms difficultly soluble compounds with mercury salts.¹⁶

Secondary and tertiary ethylenic alcohols undergo rearrangement to α - β -unsaturated primary alcohols under the action of acid reagents:



Compounds $\text{RCHXCH} = \text{CH}_2$, in which X is an acid forming group, undergo a similar rearrangement. The ease of transformation in this case increases with the strength of the acid HX, or the ionic stability of X, the ionizing power of the medium, and the degree of negativity of R.¹⁴³

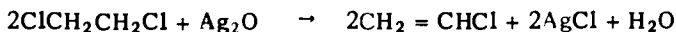
Isopropenyl vinyl carbinol rearranges in the following manner:



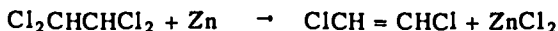
Unsaturated Halides

The reaction of halogens with olefin hydrocarbons generally results in the formation of addition compounds, although under certain conditions substitution may take place without addition at the double bond.

The treatment of a di- or polyhalo compound with silver oxide generally yields a halo olefin:

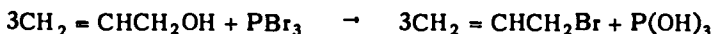


Halo olefins may also be obtained by dehalogenating polyhalo compounds with zinc or iron filings:¹⁷



Almost all the possible brominated ethylenes have been prepared by dehalogenating the various brominated ethanes.¹⁸ Bromoethylene, $\text{CH}_2 = \text{CHBr}$, has been obtained from dibromoethane; *asym*-dibromoethylene, $\text{CH}_2 = \text{CHBr}$, has been made from tribromoethane, $\text{CH}_2\text{BrCHBr}_2$, tribromoethylene, from *asym*-tetrabromoethane, and tetrabromoethylene from pentabromoethane.

Unsaturated halides may be obtained by replacing the hydroxy group in unsaturated alcohols with a halogen atom by reaction with a phosphorus halide:

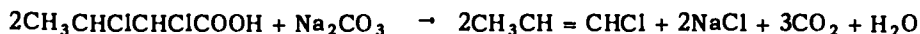


They may be obtained, furthermore, by replacing the oxygen of a saturated carbonyl compound with two halogen atoms by reaction with a phosphorus halide, and subsequently dehydrohalogenating the product:¹⁹



The dihalides may often be dehydrohalogenated simply by boiling.

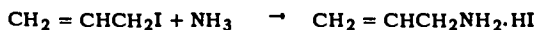
Some unsaturated halides may be obtained by heating dihalo carboxylic acids with alkali carbonates:²⁰



This reaction always leads to the formation of compounds in which the halogen is attached to a carbon atom with a double bond. Bromostyrene, $\text{C}_6\text{H}_5\text{CH} = \text{CHBr}$, and substituted bromostyrenes have been prepared by this method from cinnamic acid and substituted cinnamic acids via the dibromo compounds obtained by the addition of bromine.²¹

Chemical Behavior of Unsaturated Halides

The halogen in allyl halides and in other β -halo olefins is reactive and may be replaced with various negative groups,²² reaction with amines giving unsaturated amines:



With sodium ethoxide, ethyl ethers of the corresponding olefin alcohols are obtained.

Allyl bromide combines with tertiary amines with appreciable evolution of heat to form a quaternary ammonium bromide, whereas α - and β -bromopropylenes, $\text{CH}_3\text{CH} = \text{CHBr}$ and $\text{CH}_3\text{CHBr} = \text{CH}_2$, react to form allylene, $\text{CH}_3\text{C} \equiv \text{CH}$.²³

The halogen in vinyl halides and in other halo compounds in which the halogen is attached to an unsaturated carbon atom is unreactive. Thus, vinyl bromide does not give vinyl ethyl ether with sodium ethoxide but reacts only at high temperatures with this compound to form acetylene. Vinyl bromide fails to react with silver acetate at 100° , and with sodio malonic ester at 170 – 180° ;²⁴ it does not react with potassium or silver cyanide on long heating.²⁵

The reaction of hydrobromic acid with α -bromo olefins takes place with greater difficulty than with β -derivatives, both compounds giving dihalo derivatives. Both bromides yield allylenes when treated with alcoholic caustic. This is in contrast with the behavior of allyl halides which give principally allyl ether when treated with alcoholic caustic, with a small amount of allene, $\text{CH}_2 = \text{C} = \text{CH}_2$.

Diiodoethylene and chloriodoethylenes combine with chlorine to form unstable iodo dichlorides, $\text{ICH} = \text{CHICl}_2$, $\text{ClCH} = \text{CHICl}_2$; these may be converted to iodoso, iodo and iodonium compounds.²³

The chlorine in chloro fluoro compounds may be removed preferentially by dehalogenation with zinc dust suspended in alcohol, acetone, pyridine or dioxane.¹⁴⁴ Tetrafluoroethylene has been obtained by this method from *sym*-tetrafluorodichloroethane, perfluorobutadiene, $\text{F}_2\text{C} = \text{CFCH} = \text{CF}_2$ from *sym*-hexafluorotetrachlorobutane, and hexafluorobutene, $\text{F}_3\text{CCH}_2\text{CF} = \text{CF}_2$, from 1,2-dichlorohexafluorobutane.

Tetrafluoroethylene is best prepared by the pyrolysis of difluorochloromethane at $600\text{--}1000^\circ$ in a carbon, silver, or platinum tube. Yields of 90 to 95% have been reported.¹⁴⁵

Vinyl fluoride has been obtained in 82% yield by the addition of elements of hydrogen fluoride to acetylene.¹⁴⁶

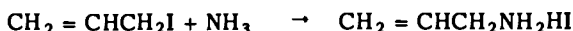
The double bond in tetrafluoroethylene has been shown to react with alcohols in the presence of basic catalysts to form ethers.¹⁴⁷

Monohaloethylenes show a strong tendency to polymerize.²⁶

Sym-dihaloethylenes have been obtained in two geometric isomers which are easily interconvertible. The *cis* isomer is dehydrohalogenated appreciably more easily than the *trans* isomer.²⁷

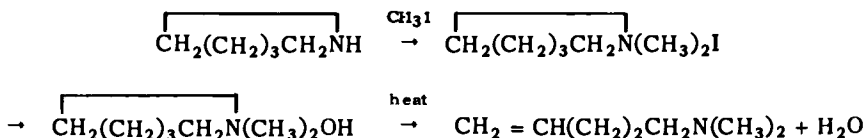
Unsaturated Amines

Certain unsaturated amines may be prepared by the reaction of unsaturated compounds having a reactive halogen, such as allyl iodide, with ammonia or amines:



Unsaturated amines have also been obtained by dehydrohalogenation of certain halo amines. Isoallylamine, $\text{CH}_3\text{CH} = \text{CHNH}_2$, has been obtained, for example, from β -bromopropylamine,²⁸ and propargylamine, $\text{CH} \equiv \text{CCH}_2\text{NH}_2$, from dibromoallylamine, $\text{BrCH}_2\text{CHBrCH}_2\text{NH}_2$,²⁹ by treatment with potassium hydroxide.

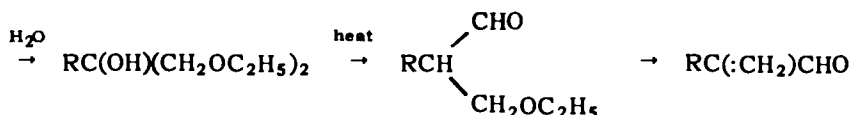
Cyclic amines may be converted to unsaturated amines by the Hofmann degradation.³⁰ Piperidine, for example, may be degraded to desdimethylpiperidine by the following series of reactions:



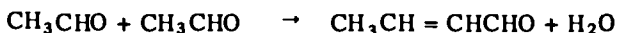
Unsaturated Aldehydes

Homologs of acrolein may be prepared through the reaction of chloromethyl ethyl ether with fatty acid esters and magnesium in the presence of some mercuric chloride, and heating the resulting hydroxy ether with anhydrous oxalic acid:³¹



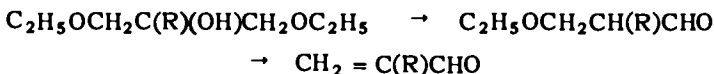


Acrolein homologs may also be obtained through the self-condensation of saturated aldehydes under the action of zinc chloride, formic acid, sodium acetate, secondary amines,³² and other reagents:



In this reaction, the carbonyl group in one molecule of the aldehyde reacts with the methyl or methylene group adjacent to the carbonyl in the other.³³ Such aldehydes may also be obtained by the dehydration of aldols.

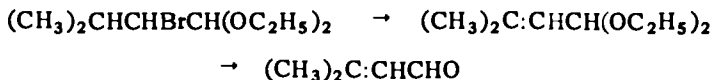
Pyrolysis of dialkyl ethers of glycerine or homologs of glycerine in the presence of anhydrous oxalic acid results in the formation of unsaturated aldehydes:³⁴



The general method of preparation of aldehydes which depends on the distillation of the calcium salt of a carboxylic acid with calcium formate is applicable to the preparation of unsaturated aldehydes, and citral has been obtained by this method from a mixture of calcium geranate and calcium formate.

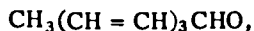
Allylic hydroxy compounds, $\text{RR}'\text{C}(\text{OH})\text{CH}_2\text{CH}=\text{CH}_2$, obtained from ketones $\text{RR}'\text{CO}$ and allyl bromide via the Grignard compound or Reformatsky's reaction may be converted to the hydroxy aldehydes $\text{RR}'\text{C}(\text{OH})\text{CH}_2\text{CHO}$ by ozonization followed by reductive cleavage, and these may be converted to the unsaturated aldehydes $\text{RR}'\text{C}:\text{CHCHO}$ by dehydration.³⁵

Methylcrotonaldehyde has been prepared from ethyl α -bromovaleracetal by debromination and hydrolysis:³⁶



Polyene Synthesis

Aldehydes with more than one double bond in their molecule may be obtained by the repeated self-condensation of aldehydes, the unsaturated aldehyde first formed reacting further with one or more molecules of the original saturated aldehydes. Thus, sorbaldehyde, $\text{CH}_3(\text{CH}=\text{CH})_2\text{CHO}$, and octatrieneal,



have been prepared from acetaldehyde, or acetaldehyde and crotonaldehyde, by condensing these compounds in the presence of piperidine. Dodecapentaneal, $\text{CH}_3(\text{CH}=\text{CH})_5\text{CHO}$, has been obtained in 12.5% yield through the condensation of crotonaldehyde with octatrieneal in the presence of piperidine acetate;³⁷ the compound has been obtained in an appreciably higher yield by carrying out

the condensation in the presence of a large quantity of the catalyst.³⁸

The self-condensation of methylcrotonaldehyde induced by piperidine acetate or barium hydroxide results in the formation of open chain polyene aldehydes, such as fornesial, $\text{CH}_3[\text{C}(\text{CH}_3)=\text{CHCH}=\text{CH}]_2\text{C}(\text{CH}_3)=\text{CHCHO}$, and dehydrocitril, $(\text{CH}_3)_2\text{C}=\text{CHCH}=\text{CHC}(\text{CH}_3)=\text{CHCHO}$.³⁹ The compound gives the cyc-

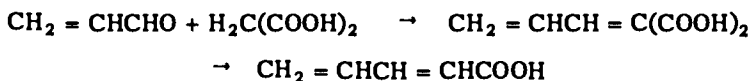
lic unsaturated aldehyde $(\text{CH}_3)_2\text{CCH}_2\text{C}(\text{CH}_3):\text{CHCH}:\text{CCHO}$, although in very low yield, when the condensation is carried out in the presence of sodamide.

The condensation of acetaldehyde with citral in the presence of piperidine acetate or sodamide results in the formation of citrilidene acetaldehyde,



in 30% yield.⁴⁰

Polyene carboxylic acids may be prepared through the condensation of unsaturated aldehydes with malonic acid in the presence of piperidine and subsequent decarboxylation:



Condensation of the half diphenylene amide of malonic acid with an aldehyde, followed by reduction of the product with lithium aluminum hydride results in the formation of an unsaturated aldehyde with two carbon atoms more than the original aldehyde. The method has been employed for the preparation of polyene aldehydes.¹⁴¹

Chemical Behavior of Unsaturated Aldehydes

Oxidizing agents even of the mildest type convert only a small portion of unsaturated aldehydes into the corresponding unsaturated acids. Thus, methylacrolein gives some methylacrylic acid on oxidation, together with dihydroxycaproic acid, and several cleavage products, including propionic and acetic acids.

Sulfurous acid adds readily at the double bond of acrolein and homologs of this aldehyde. Since reaction with the carbonyl group takes place simultaneously, the products obtained are the bisulfite addition compounds of the saturated sulfonic aldehyde. The free sulfonic aldehyde may be obtained from the reaction product of sulfurous acid and crotonaldehyde by boiling in aqueous solution:⁴¹



α -Monoalkyl acrolein gives the normal aldehyde bisulfite compound, however, the unsaturated bonds remaining intact; the unsaturated aldehyde may be freed from the bisulfite compound by treatment with sodium carbonate solution.⁴²

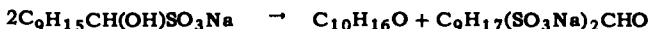
The normal bisulfite compound of *citronellal* is obtained in the crystalline form upon shaking the aldehyde with 35% solution of sodium bisulfite. When, however, citronellal is made to react with a sufficient quantity of sodium bisulfite in the presence of some sodium sulfite, then both the carbonyl group and the double bond are attacked, and the dihydrosulfonic derivative of citronellal,



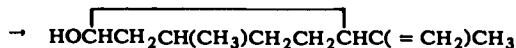
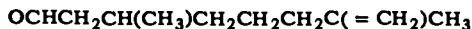
is formed, from which dihydrocitronellalsulfonic acid is obtained by warming with dilute caustic.

Hydrocyanic acid reacting with unsaturated aldehydes gives unsaturated cyanohydrins.⁴³

The normal bisulfite compound of *citral*, $\text{C}_9\text{H}_{15}\text{CH}(\text{OH})\text{SO}_3\text{Na}$, results in quantitative yield when the aldehyde is made to react with a solution of sodium bisulfite to which a little acetic acid has been added. Citral cannot be wholly recovered from the bisulfite compound, however, and the product decomposes on distillation with steam in the following manner:⁴⁴

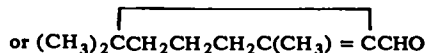
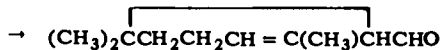


Citronellal may be readily converted to a cyclic isomer, *isopulegol*:



The transformation takes place, for example, on heating the aldehyde with acetic anhydride, isopulegol being then obtained as its acetic ester. The transformation also takes place on long storage.

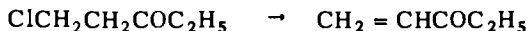
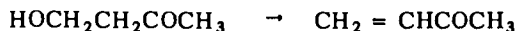
This ability of forming cyclic isomers is shared by many other olefinic terpenes. Citral, for example, may be converted to a cyclic alcohol:



This transformation of citral does not proceed readily, but derivatives of citral in which the aldehyde group has been deactivated by substituents isomerize in this manner readily.

Unsaturated Ketones

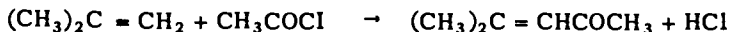
α,β -Unsaturated ketones may be obtained through the dehydration of 1,3-keto alcohols, or dehydrohalogenation of β -halo ketones with diethylaniline:⁴⁵



The dehydration of aldol type of compounds obtained through the interaction of

aldehydes and ketones, or of ketones among themselves may be considered a modification of this method.⁴⁶

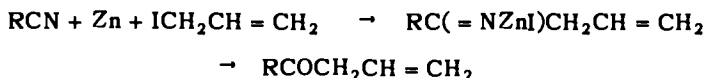
Unsaturated ketones are formed through the condensation of certain olefin hydrocarbons with acid chlorides in the presence of aluminum chloride:⁴⁷



In this reaction, an addition product is apparently first formed,⁴⁸ and is dehydrohalogenated, as it is formed, to the olefinic ketone, providing the temperature is maintained sufficiently high during the reaction.

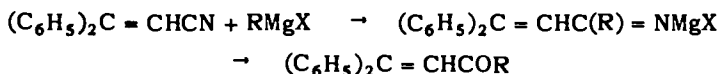
In a few instances α,β -olefinic ketones have been obtained by the reaction of α,β -olefin carboxylic acid chlorides with zinc alkyls.⁴⁹

Allyl alkyl ketones result through the reaction of nitriles with allyl iodide and metallic zinc and subsequent hydrolysis of the reaction product:⁵⁰



Such ketones are readily converted to propenyl alkyl ketones, $\text{RCOCH} = \text{CHCH}_3$, under the action of mineral acids.

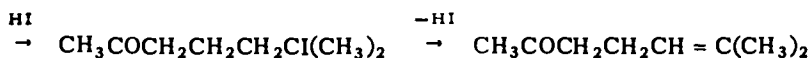
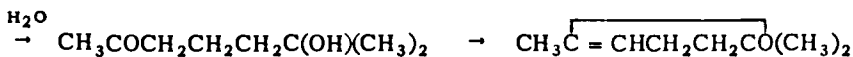
α,β -Unsaturated nitriles with a substituent in the β -position react normally with Grignard reagents to form halomagnesium ketimes which on hydrolysis yield α,β -unsaturated ketones:⁵¹



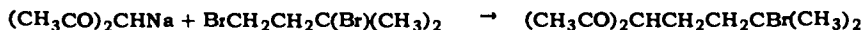
Unsaturated nitriles of the type $\text{R}'\text{CH} = \text{CHCN}$ yield β -substituted nitriles by reaction with Grignard reagents:



Hydroxy ketones obtained by Reformatsky's reaction from iodo ketones and carbonyl compounds may be transformed into lactones which may be converted to unsaturated ketones by reaction with hydriodic acid followed by decomposition with alkali. The sequence of reactions with acetone and γ -iodopropyl methyl ketone, which gives methyl heptenone, is as follows:



The product of the reaction of the sodium derivative of acetylacetone with certain dihalo compounds may be converted to unsaturated ketones by treatment with alkali; methyl heptenone has been obtained by this method, for example, from 2-methyl-2,4-dibromobutane:



Certain unsaturated keto acids may be decarboxylated to olefinic ketones; vinyl methyl ketone, $\text{CH}_2=\text{CHCOCH}_3$ may be obtained, for example, from β -acetylacrylic acid, $\text{CH}_3\text{COCH}=\text{CHCOOH}$, by distillation under ordinary pressure, and heptachloro-ethylideneacetone, $\text{Cl}_2\text{CHCCl}=\text{CClCOCCl}_3$, has been obtained from trichloroacetyl-tetrachlorocrotonic acid by heating with water.⁵²

Reactions of Olefinic Ketones

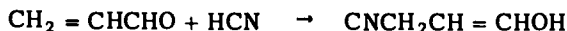
The reactions common to unsaturated compounds are shown by olefinic ketones. The proximity of the carbonyl group activates the unsaturated linkage markedly in α,β -unsaturated ketones.⁵³

Bromine readily adds to the unsaturated bonds in α,β -olefinic ketones; the resulting compounds readily release hydrogen bromide to form α -bromo olefinic ketones, which yield α -diketones on hydrolysis.⁵⁴

Hydrocyanic acid occasionally adds at the double bond of some unsaturated ketones, as well as at the carbonyl group. This occurs with ethyl vinyl ketone, $\text{C}_2\text{H}_5\text{COCH}=\text{CH}_2$, which yields the saturated cyanocyanhydrin,



1,4-Addition often takes place with α,β -unsaturated carbonyl compounds, resulting in the formation of an unsaturated hydroxy nitrile:



Addition compounds are formed readily with *hydrogen halides* and α,β -unsaturated ketones, the halogen atom entering the β -position.

Sulfurous acid also sometimes adds both to the carbonyl group and the unsaturated bonds.

Phorone reacts slowly with sodium bisulfite to form the compound



which cannot be reconverted to phorone by treatment with cold sodium carbonate solution, although conversion may be accomplished by treatment with concentrated alkali, or by dry-distillation.

Mercaptans give mercaptoles and mercaptomercaptoles with unsaturated ketones. Thus, propenyl methyl ketone gives $\text{CH}_3\text{CH}:\text{CHC}(\text{SC}_2\text{H}_5)_2\text{CH}_3$ and $\text{CH}_3\text{CH}(\text{SC}_2\text{H}_5)\text{CH}_2\text{C}(\text{SC}_2\text{H}_5)_2\text{CH}_3$ with methyl mercaptan. Phorone gives only a dimercaptoketone, $(\text{CH}_3)_2\text{C}(\text{SC}_2\text{H}_5)\text{CH}_2\text{COCH}_2\text{C}(\text{SC}_2\text{H}_5)(\text{CH}_3)_2$, with ethyl mercaptan.⁵⁶

Malonic ester, acetoacetic ester, and other similar compounds with reactive methylene are capable of forming addition compounds with α,β -olefinic ketones the organic group attaching itself to the β -carbon atom, ketones of the type $\text{RCOCH}=\text{CHR}$ giving $\text{RCOCH}_2\text{CHRCH}(\text{COOC}_2\text{H}_5)_2$ with malonic ester.

Aryl magnesium halides are also capable of reacting with the unsaturated bond in such ketones, the products giving on hydrolysis aryl substituted tertiary alcohols or saturated ketones.⁵⁷

Ammonia, primary and secondary amines readily add to unsaturated ketones to form β -amino ketones.⁵⁸

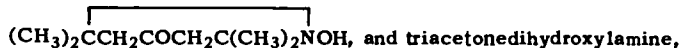
Ammonia, reacting with mesityl oxide or phorone gives the bases diacetoneamine, triacetoneamine, and triacetonediamine. These compounds are also obtained through the reaction of acetone and ammonia.⁵⁹ Phorone reacting with primary amines gives *N*-alkyl acetoneamines.⁶⁰

Hydroxylamine gives with α,β -unsaturated ketones the normal unsaturated oxime and β -hydroxylamino oxime, $\text{RCH}(\text{NHOH})\text{CH}_2\text{C}(\text{:NOH})\text{R}'$. Similarly, semicarbazide gives the unsaturated semicarbazone and the semicarbazido carbazone.⁶¹ Hydrazines react both with the carbonyl group and the unsaturated bonds forming cyclic pyrazolines.

Mesityl oxide reacting with hydroxylamine in methyl alcoholic solution in the presence of sodium methylate gives principally diacetone hydroxylamine,



In cold alcoholic solution, in the presence of sodium carbonate, α -mesityloxime, $(\text{CH}_3)_2\text{C} = \text{CHC}(\text{:NOH})\text{CH}_3$, is formed. With phorone, triacetonehydroxylamine,

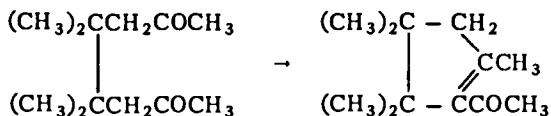


are obtained.

The unsaturated bond in α,β -olefinic ketones is reduced in preference to the carbonyl group, and for this reason it is impossible to prepare α,β -unsaturated alcohols from the corresponding olefinic ketones by reduction.⁵⁶ When a mild reducing agent, such as aluminum amalgam is employed, dimolecular condensation products are obtained:

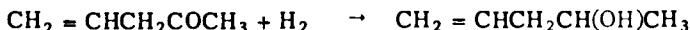


Diketones of this type resulting from aliphatic ketones are unstable and undergo transformation to cyclic monoketones with loss of a molecule of water:⁶²



Diketones of the same type derived from aromatic α,β -unsaturated ketones are stable.

Ketones in which the unsaturated bond is situated at the β,γ -position, or is further removed from the carbonyl group are readily converted to olefinic alcohols by reduction with sodium and alcohol.⁶³



Catalytic reduction in the presence of active nickel at 180-190° yields the saturated ketone.⁶⁴

Allyl ketones $\text{RCOCH}_2\text{CH}=\text{CH}_2$ in which R is a methyl, ethyl or propyl group are converted by mineral acids into propenyl ketones, $\text{RCOCH}=\text{CHCH}_3$.

Vinyl and isopropenyl methyl ketones, $\text{CH}_3\text{COCH}=\text{CH}_2$ and



are readily polymerized.⁶⁵

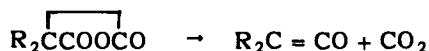
Ketenes

Ketenes have been usually prepared through the dehalogenation of α -halo acid chlorides with zinc or other metals in a non-hydroxylic solvent:

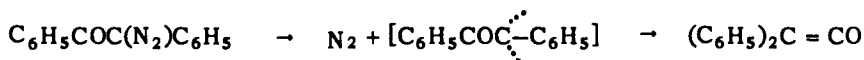


Diphenyl and dimethylketene, among others, have been prepared by this method.

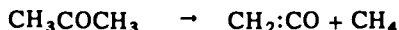
Another general method consists in heating substituted malonic anhydrides:⁶⁶



Ketenes are obtained also by heating diazo derivatives of carbonyl compounds:



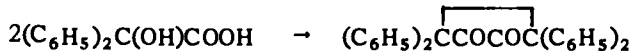
Ketene itself has been obtained by the pyrolysis of acetone vapors at dark red heat:⁶⁷



The compound has also been prepared by the pyrolysis of acetic anhydride, by passing its vapors over a glowing platinum wire:⁶⁸



A dimeric ketene, 3,3,4,4-tetraphenylcyclobutane-1,1-dione, results on heating benzoic acid in the presence of a little sodium carbonate:⁶⁹



Carbon suboxide has been made by heating malonic ester with phosphorus pentoxide:⁷⁰



Reactions of Ketenes

The presence of adjacent double bonds in the molecule renders ketenes highly reactive toward many compounds. They combine with water, alcohols, amines, and other classes of compounds.⁷¹

Water converts ketenes to acids:



The reaction takes place readily, and serves to determine ketenes quantitatively by titrating the acid formed with standard alkali. Hydrolysis may be carried out, for this purpose, in ether or in pure ethyl acetate.

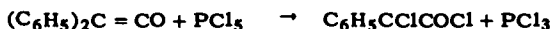
Esters are formed through the reaction of ketenes with *alcohols*, and amides are formed with *ammonia* and *amines*. Anhydrides are formed by reaction with *carboxylic acids*:



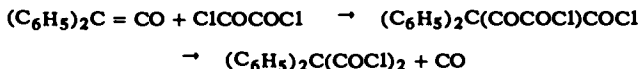
Halogens add to ketenes to form α -halo acid halides:



Phosphorus pentachloride reacting with diphenylketene gives diphenylchloroacetyl chloride:

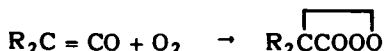


Oxalyl chloride reacts with diphenylketene to form diphenylmalonyl chloride:



Benzoyl chloride and bromide do not give addition products with diphenylketene, but cause the polymerization of the latter. Acetyl chloride is without action on ketene.

Keto ketenes, $RR'C = CO$, readily combine with oxygen. Reaction in an inert solvent at -20° results in the formation of moloxides:⁷²



When warmed to room temperature, these moloxides are decomposed with the formation of a ketone, R_2CO and liberation of carbon dioxide; or they change to polymeric products.

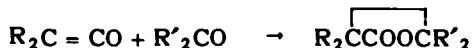
Polymeric oxides, $(R_2C - CO)_x$, known as ketene oxides, result when oxygen



is conducted through an ethereal solution of ketene at room temperature, the oxide precipitating out as a solid.

Aldo ketenes do not show the ready tendency of keto ketenes to combine with oxygen.

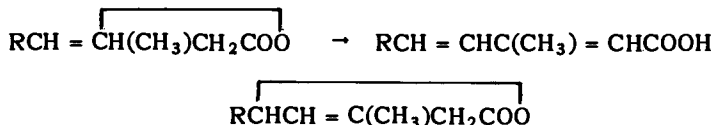
Ketenes combine with many unsaturated compounds.⁷³ They are capable, in particular, of combining with carbonyl compounds to form lactones:⁷⁴



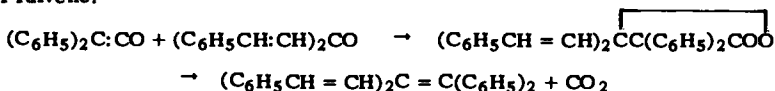
Many catalysts have been used. Boric acid, triacetyl borate, zinc thiocyanate, and zinc chloride are to be preferred for the reaction with aldehydes, and boron trifluoride etherate for the reaction with ketones. The reaction is carried out at 0 to 10° in order to minimize the formation of polymeric products. Yields of

lactones from formaldehyde and acetaldehyde are 85% of theory. The carbonyl group reacts with ketenes less readily than the group $=C:N-$, reaction taking place only when the group is activated by doubly bound atoms. The β -lactones formed are often unstable and decompose into a hydrocarbon and carbon dioxide.

The lactones formed from conjugated olefinic ketones decompose to dienic acids which isomerize to olefinic δ -lactones:¹⁴⁸

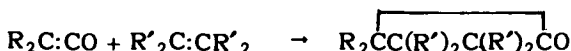


The reaction product of dibenzalacetone and diphenylketene is a compound of the type of fulvene:

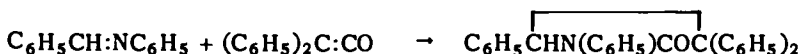


Florenone reacting with diphenylketene similarly gives diphenyldiphenylene ethylene; benzophenone gives tetraphenylethylene. Quinone yields diphenylquinomethane and tetraphenylparaxylylene.

Ketenes give cyclobutane derivatives with certain unsaturated compounds:

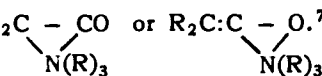


Lactams are formed by reaction with *Schiff's bases*:

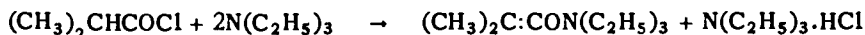


Ketenes also combine with *carbon dioxide* to form anhydrides of dicarboxylic acids, $\text{R}_2\overline{\text{CCOOCO}}$.⁷⁵

Ketenes react with certain *tertiary nitrogen bases*, such as pyridine and quinoline, to form the so-called "*ketene bases*".⁷⁶ In these compounds two molecules of ketene are combined with a single nitrogen atom, all five valences of nitrogen being satisfied by carbon bonds, a type of combination not encountered with other classes of compounds. "*Ketenium bases*", as distinct from ketene bases, are combinations of one molecule of ketene with one of the base and probably possess the structure $\text{R}_2\text{C} - \text{CO}$ or $\text{R}_2\text{C}:\text{C} - \text{O}$.⁷⁷ They are



formed through the reaction of ketenes with tertiary aliphatic bases. They may be conveniently prepared by heating the chloride of the appropriate acid with such bases:



Ketenium bases do not possess the high reactivity of ketenes.

Because of their highly unsaturated nature and the great reactivity of the unsaturated bonds, ketenes show a strong tendency to polymerize. The tendency is most marked with aldoketenes, RCH:CO , the polymerization of these compounds often proceeding very rapidly.⁷⁸ The polymerization of methyl-, phenyl- and ethylketenes proceeds so rapidly, even in dilute solution, that it is impossible to prepare these compounds in a pure form. Ketene in the pure form polymerizes at room temperature.

Many ketenes form dimeric products which are cyclic compounds with a four carbon ring, $\text{R}_2\text{CCOC(R)}_2\text{CO}$. These are often readily depolymerized to the monomeric ketene. Thus, dimethylketene results when the dimer of the compound is passed over a glowing platinum wire.⁷⁹ Depolymerization occasionally may be brought about by distilling the dimeric product.

Reactions of Ketene Acetals

The methods employed for the preparation of ketene acetals have been considered in another section. Here reactions involving ketene acetals will be considered.

The reaction of ketene acetals with water is similar to that of ketenes, and results in the formation of esters:



Primary and secondary alcohols give orthoesters with ketenes:⁸⁰



Tertiary alcohols do not give this reaction. Ketene diphenyl acetal,

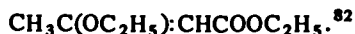


does not yield an alkyl diphenyl orthoester by reaction with alcohols, but forms triphenyl orthoacetate.⁸¹

Ketene diethyl acetal, added to an ethereal solution of an acid, gives ethyl acetate in quantitative yield:



When, however, a solution of the acid is added to the acetal, a 1,4-addition also takes place, resulting in the formation of ethyl O-ethylacetoacetate,

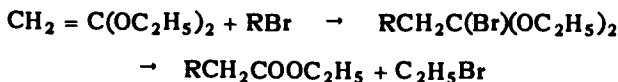


Ketene diphenylacetal polymerizes under the action of hydrobromic acid.

Amines of low basic strength react readily with ketene acetals to form acid amides, aniline, for example, giving N-phenylacetamide, $\text{CH}_3\text{CONHC}_6\text{H}_5$, in 85% yield, together with some N,N'-diphenylacetamidine, on reaction with ketene acetal at 25°. Amines of greater basic strength react less readily. Thus, ethyl aniline reacts somewhat less readily than aniline, although reaction proceeds rapidly at 100°, whereas completion of the reaction with ammonia requires

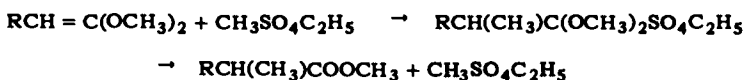
three hours at this temperature, the latter giving largely acetonitrile with some acetamidine.

Reactive *organic halides* of the type of benzyl and allyl bromides give addition products with ketene acetals which decompose to esters.⁸²

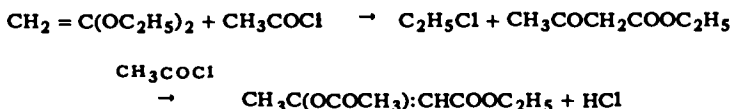


Substituted acetals, $\text{RCH} = \text{C}(\text{OC}_2\text{H}_5)_2$, are also formed in the course of the reaction, and react with the halide to give disubstituted esters, $\text{R}_2\text{CHCOOC}_2\text{H}_5$. Disubstituted ketene acetals do not appear to be formed, however. Cyanoketene methyl acetal, $\text{CNCH} = \text{C}(\text{OCH}_3)_2$, reacts with benzyl bromide to give both the mono and dibenzyl cyanoacetic esters, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{CN})\text{COOCH}_3$ and $(\text{C}_6\text{H}_5\text{CH}_2)_2\text{C}(\text{CN})\text{COOCH}_3$, the latter apparently via the benzylcyanoketene methyl acetal, $\text{C}_6\text{H}_5\text{CH}_2\text{C}(\text{CN}) = \text{C}(\text{OCH}_3)_2$.⁸³

The reaction of *n*-propylketene dimethyl acetal with *diethyl sulfate* results in the formation of methyl α -methylvalerate in 65% yield.⁸⁴ This is explained by assuming that a small amount of methyl ethyl sulfate is formed by cleavage of the initial addition product, $\text{C}_3\text{H}_7\text{—CH}(\text{C}_2\text{H}_5)\text{C}(\text{OCH}_3)_2\text{SO}_4\text{C}_2\text{H}_5$, and acts as a catalyst for the transformation of the original acetal to the methylvalerate ester by the following mechanism:

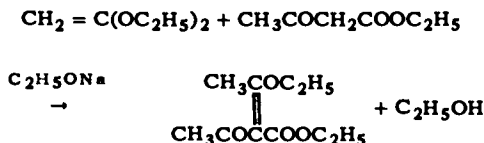


Ketene diethyl acetal reacts exothermally with an equivalent of acetyl chloride at room temperature to give *O*-acetylacetoacetic ester in 30% yield:



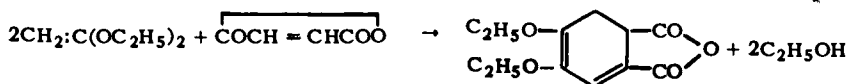
Benzoyl chloride reacts less readily, but a 59% yield of ethyl *O*-benzoylbenzoylacetate, $\text{C}_6\text{H}_5\text{C}(\text{OCOC}_6\text{H}_5):\text{CHCOOC}_2\text{H}_5$, may be obtained on heating the chloride with the acetal at 100° for two hours.⁸² Benzene sulfonyl chloride causes the polymerization of ketene acetal.

Acetoacetic ester adds to ketene ethyl acetal in the presence of a basic catalyst in the following manner:⁸⁵



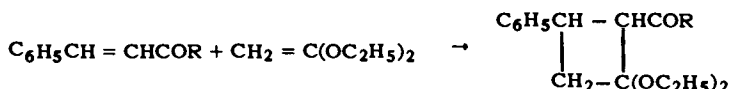
Malonic ester reacts to form the compound $\text{CH}_2 = \text{C}(\text{OC}_2\text{H}_5)\text{CH}(\text{COOC}_2\text{H}_5)_2$, while methylmalonic ester, $\text{CH}_3\text{CH}(\text{COOC}_2\text{H}_5)_2$, does not react. Dibenzoylmethane, $\text{CH}_2(\text{COC}_6\text{H}_5)_2$, reacting in the enolic form gives orthoesters with ketene acetals, forming the compound $\text{CH}_3\text{C}(\text{OC}_2\text{H}_5)_2\text{OC}(\text{C}_6\text{H}_5):\text{CHCOC}_6\text{H}_5$, with ketene ethylacetate.⁸⁶

Maleic anhydride reacting in ethereal solution with two molecules of ketene acetal, in a type of 1,4-diene addition, forms 3,5-dimethoxy-1,6-dihydrophthalic anhydride in 70% yield:



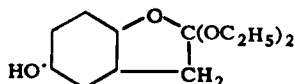
A second diene addition also takes place in benzene solution, and results in the formation of the anhydride of a tetracarboxylic acid.⁸⁷ Dimethylmaleic anhydride does not undergo this reaction.

Benzalacetophenone and *dibenzalacetone* heated with an excess of ketene acetal at 125° give a cyclobutene derivative in 87 to 91% yield:



Benzalacetone does not give a cyclobutane derivative, and *phorone* does not react.

Benzoquinone reacting at about 80° with ketene ethyl acetal in benzene solution forms an ethoxy coumarone,

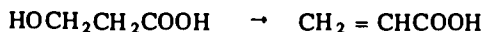


Bromobenzoquinone and 2,5-dibromobenzoquinone also react similarly, while *m*-xyloquinone gives the coumarone in poor yield and *p*-xyloquinone gives only tarry products.⁸⁸

Unsaturated Acids

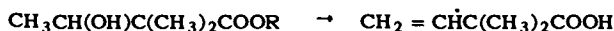
Methods of Preparation

Unsaturated acids may be prepared by most of the general methods employed for the preparation of unsaturated compounds. α,β -Unsaturated acids may be obtained, for example, through the dehydration of α - and β -hydroxy acids:⁸⁹

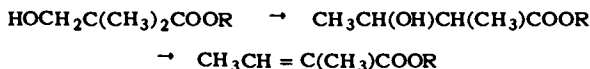


The β -hydroxy acids are dehydrated with particular ease, simply by heating to about 100°, or by heating with caustic.⁹⁰ α -Hydroxy acids are best dehydrated by esterification followed by heating with phosphorus trichloride. The nitriles of these acids may be dehydrated by heating with phosphorus pentoxide.⁹¹

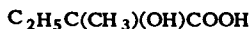
β -Hydroxy acid esters with one or more substituents in the α -position, heated with phosphorus pentoxide, give β,γ -unsaturated acids:



Acids in which a carbon atom is not already present in the γ -position undergo a molecular rearrangement resembling retropinacoline transformation preceding dehydration:⁹²

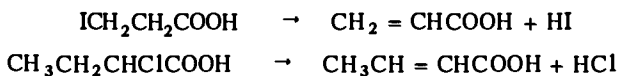


Tiglic acid, $\text{CH}_3\text{CH}:\text{C}(\text{CH}_3)\text{COOH}$, results from methylethylhydroxyacetic acid,



Vinyl dimethylacetic ester, $\text{CH}_2 = \text{CHC}(\text{CH}_3)_2\text{COOC}_2\text{H}_5$, results when α, α, β -trimethylmalic ester, $\text{C}_2\text{H}_5\text{OCOC}(\text{OH})(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{COOC}_2\text{H}_5$, is heated with phosphorus pentoxide. γ, γ, γ -Trichlorocrotonic acid results when trichlorohydroxybutyric acid is boiled with sodium acetate and acetic anhydride.⁹³

Unsaturated acids are formed also through the dehydrohalogenation of halo acids:



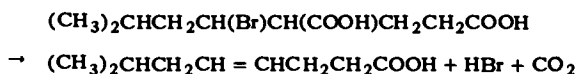
The reaction takes place with ease even when the halogen is attached to a tertiary carbon atom. α -Halo acids may be obtained directly through the halogenation of saturated acids. Dehydrohalogenation occasionally takes place by simple warming,⁹⁴ but generally treatment with alcoholic caustic is necessary.⁹⁵ Exchange of the halogen with a hydroxy or ethoxy group often takes place during dehydrohalogenation. This may be avoided by employing a tertiary base instead of caustic.⁹⁶

Halo acids with more than four carbon atoms in the chain yield α, β - as well as β, γ -unsaturated acids. The latter are apparently formed through the addition of hydrogen halide to the former and subsequent dehydrohalogenation of the resulting halo acid.⁹⁷ γ -Halo acids yield lactones by the treatment.

α -Alkyl α -bromosuccinic acids heated in alkaline solution yield unsaturated acids:⁹⁸



Acids with a bromine atom at the β -position behave similarly:⁹⁹

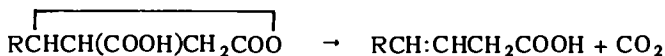


α, β -Unsaturated acids may be obtained from α, β -dihalo acids. The transformation is brought about by reduction with nascent hydrogen, or by heating with potassium iodide solution:

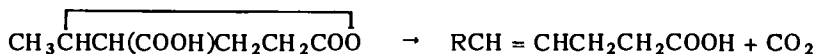


Heated with sodium hydroxide, α, β -dichloropropionic acid decomposes to chloropropylene, $\text{CH}_3\text{CH}:\text{CHCl}$.

Lactones of certain hydroxy dicarboxylic acids are converted to monobasic unsaturated acids by distillation. Unsaturated acids are obtained, for example, by this procedure from α -allylparaconic acid:¹⁰⁰



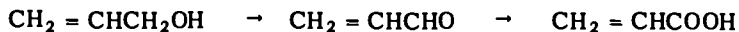
Decarboxylation of this type takes place also with δ - and ϵ -lactones, resulting in the formation of unsaturated acids.¹⁰¹



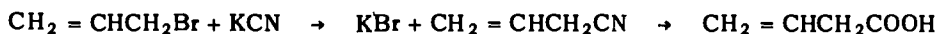
Unsaturated acids may be prepared by many of the methods employed for the

preparation of acids by using unsaturated derivatives as the primary materials.

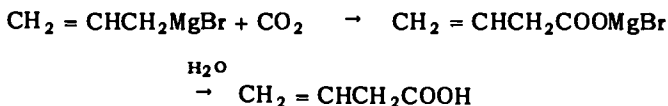
Unsaturated acids may be prepared, for example, through the oxidation of olefinic alcohols or aldehydes with mild oxidizing agents, such as atmospheric oxygen or silver oxide:¹⁰²



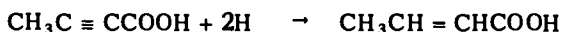
β,β -Dimethylacrylic acid, $(\text{CH}_3)_2\text{C} = \text{CHCOOH}$, is obtained by treating mesityl oxide with sodium hypochlorite.¹⁰³ Olefinic acids may be obtained also from unsaturated halides and potassium cyanide by hydrolyzing the nitrile formed:



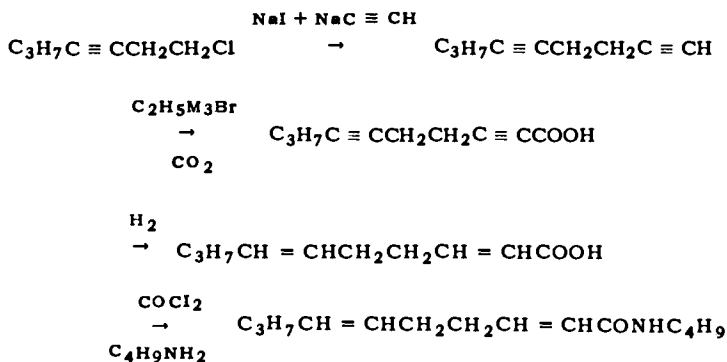
Unsaturated acids result, further, through the reaction of unsaturated organo-magnesium compounds with carbon dioxide:¹⁰⁴



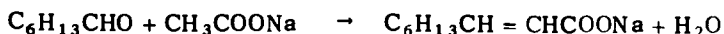
Partial reduction of acetylenic acids leads to the formation of olefinic acids:¹⁰⁵



Affin has been synthesized from chloroethylpropylacetylene by condensation with sodium acetylide, conversion of the halomagnesium derivative of the resulting diacetylenic body to a carboxylic acid by reaction with carbon dioxide, followed by reduction to the corresponding diethylenic acid. Conversion to the acid chloride with phosgene and reaction of the chloride with butylamine gave the desired product:¹⁴⁹



Some unsaturated acids have been prepared by the *Perkin synthesis* i.e., through the condensation of aldehydes with the sodium salt of an acid in the presence of acetic anhydride:¹⁰⁶



This reaction proceeds well in the aromatic series, but takes place in a rather unsatisfactory manner with compounds of the aliphatic series.

Olefinic acids may also be prepared through the condensation of aldehydes

or ketones with malonic acid, in the presence of pyridine or other bases, and partial decarboxylation of the resulting dicarboxylic acids:¹⁰⁷

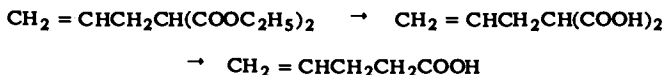


Amino acids subjected to exhaustive methylation, followed by elimination of the amino group, give unsaturated acids.¹⁰⁸

An olefinic acid result by the "acid hydrolysis" of allylacetoacetic ester:¹⁰⁹



and through the decarboxylation of allylmalonic acid:



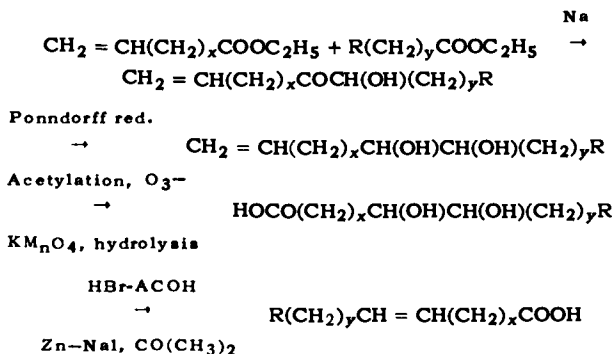
Butadienecarboxylic acid, $\text{CH}_2 = \text{CHCH}_2 = \text{CHCOOH}$, is obtained through the reduction of perchlorobutadiene carboxylic acid, $\text{Cl}_2\text{C} = \text{CClCCl}:\text{CClCOOH}$, and of perchlorobutyne carboxylic acid, $\text{Cl}_3\text{CC} \equiv \text{CCC}_2\text{COOH}$, the latter resulting from the treatment of hexachlorocyclopentanone with alkali.¹¹⁰

β -Chloroacrylic acid, $\text{ClCH} = \text{CHCOOH}$, is obtained, together with dichloroacrylic acid through the reduction of chloralid, $\text{Cl}_3\text{CCH} \begin{array}{c} \diagup \text{O} \diagdown \\ \diagdown \text{CO}_2 \diagup \end{array} \text{CHCCl}_3$, with zinc and hydrochloric acid.¹¹¹ This acid is obtained also by adding a molecule of hydrogen chloride to propiolic acid.¹¹²

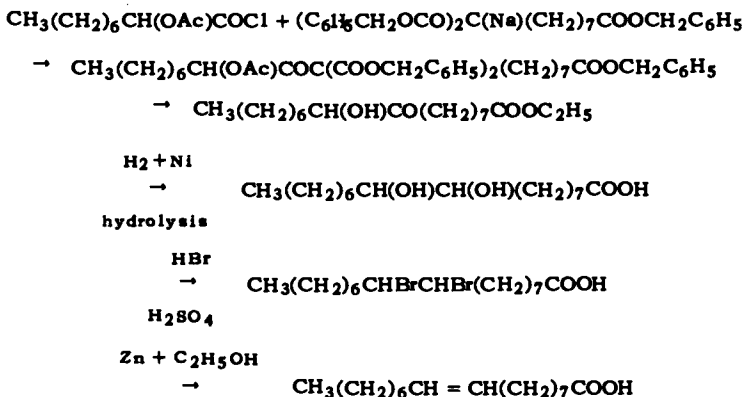
Dichloromaleic acid, $\text{HOCOCl} = \text{CClCOOH}$, is obtained in the form of its sodium salt by the reaction of aqueous sodium hydroxide with hexachloro-p-diketocyclohexene,



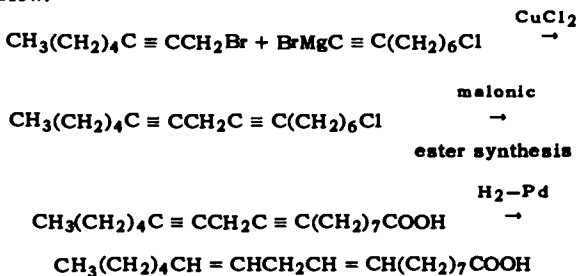
A mixed acyloin condensation of an unsaturated ester and a saturated ester yields an unsaturated acyloin from which an unsaturated acid may be prepared by the steps indicated schematically below:¹⁵⁰



A general method for the synthesis of monoolefinic acids involves the reaction of an alkyl substituted acetoacetic acid chloride with the sodio derivative of the benzyl ester of a substituted malonic acid.¹⁵¹ The method may be illustrated by the preparation of heptadec-9-enoic acid, indicated schematically below:



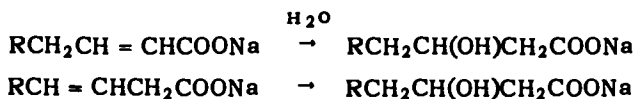
The Boord synthesis has been applied to the preparation of oleic acid.¹⁵² Linoleic acid has been synthesized by a coupling reaction from an acetylenic Grignard compound having a six carbon chain with a chlorine atom at the end of the chain attached to the acetylenic group.¹⁵³ This condensation and the steps following it are indicated schematically below:



Polyne acids have been synthesized by the standard acetylenic coupling reactions.¹⁵⁴

Reactions of Unsaturated Acids

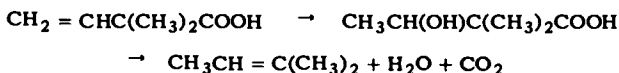
Unsaturated acids undergo the usual reactions of unsaturated compounds. The elements of water may be added readily to α,β - and β,γ -unsaturated acids under the action of boiling aqueous alkali:



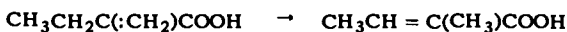
The β,γ -unsaturated acids are not hydrated by this treatment but partially isomerize to α,β -unsaturated acids.¹⁵⁴ The double bond in other olefinic acids is also displaced and migrates toward the carboxyl group when the acids are boiled with aqueous alkali. The addition of water to unsaturated bonds of higher olefinic acids is effected by treatment with concentrated sulfuric acid.¹¹⁶ When β,γ -unsaturated acids are treated at 140° for a few minutes with sulfuric acid diluted with an equal volume of water, they are converted to γ -lactones, while α,β -unsaturated acids are not changed by this treatment.¹¹⁷ Lactone

formation from β,γ -unsaturated acids takes place in some instances on simply heating the acid.

A double bond in the β,γ -position, situated at the end of a chain in an acid, migrates to the α,β -position on boiling with 1:1 sulfuric acid.¹¹⁸ Alkylated derivatives of acids of the type $\text{CH}_2 = \text{C(R)}\text{C}(\text{CH}_3)_2\text{COOH}$ take up a molecule of water and are subsequently dehydrated and decarboxylated to ethylenic hydrocarbons:

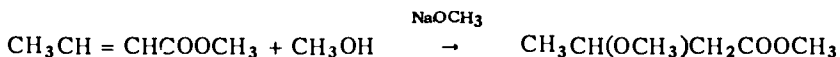


α,β -Unsaturated acids are isomerized when heated with 80 to 100% sulfuric acid at water bath temperature for a few hours. If the double bond is located in a short branch chain, it migrates into the longer chain:



The double bond migrates further, to the β,γ -position, and lactone formation then follows. It is possible that addition of water at the double bond and subsequent dehydration of the hydroxy acid formed account for the changes in the position of the double bond.

Primary and secondary alcohols and phenols may be added to α,β -unsaturated acids by treatment with boiling alcohol containing sodium alcoholate in solution.¹¹⁵

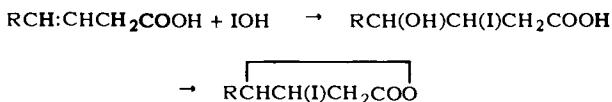


Similarly primary and secondary alcohols may be made to react with acrylonitrile to form β -alkoxypropionitriles.¹⁴⁰ Potassium hydroxide, sodium methoxide and a 40% aqueous solution of trimethylammonium hydroxide (Triton B) have been used as catalysts.

α,β -Unsaturated acids readily add *hydrogen halides*. Hydrogen bromide reacting with these acids gives the β -bromo acids, whereas with the β,γ - and γ,δ -unsaturated acids the γ -bromo acids are obtained.

Hypochlorous acid adds at the double bond of unsaturated acids, generally forming the two isomeric chlorohydroxy acids simultaneously.

The α,β - and β,γ -acids can be differentiated occasionally through the differing action of nascent *hypiodous acid* produced by the reaction of iodine with moist silver oxide or with an alkali carbonate. The α,β -unsaturated acids do not react with this reagent, while the β,γ -unsaturated acids give iodolactones:

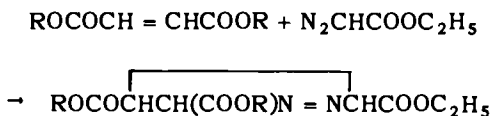


These lactones are insoluble in aqueous sodium carbonate and may, therefore, be isolated without difficulty. The original unsaturated acid may be regenerated from the iodolactone by treatment with zinc and acetic acid.

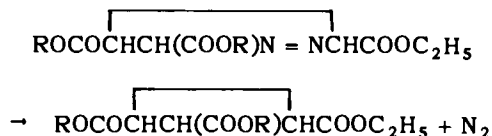
Many olefin carboxylic acids combine with *ammonia* to form amino acids.

β -Aminobutyric acid is obtained, for example, from crotonic acid. Hydroxylamine, hydrazine, and phenylhydrazine also add at the double bond of olefin carboxylic acids.

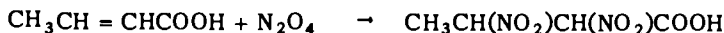
Diazomethane and *diazoacetic ester* react additively with olefin carboxylic esters to form pyrazoline carboxylic esters:¹¹⁹



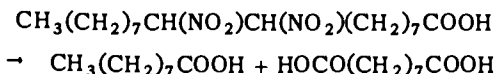
These compounds may be decomposed to cyclotrimethylene derivatives:



Nitrogen peroxide reacts with unsaturated acids to form dinitro carboxylic acids:¹²⁰



Heated with concentrated hydrochloric acid, such dinitro acids are decomposed with cleavage of the carbon chain and the formation of mono- and dicarboxylic acids. Pelargonic and azelaic acid are obtained, for example, from the nitrated product resulting from oleic acid:

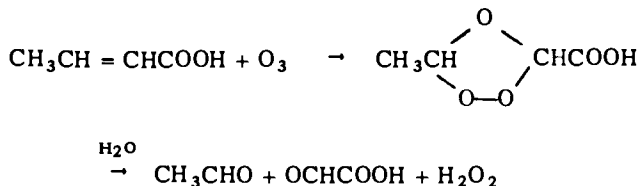


Oxidizing agents, such as chromic acid, nitric acid, or potassium permanganate, attack the double bond of unsaturated acids causing cleavage of the molecule at this point, and giving mono and dicarboxylic acids. Dihydroxycarboxylic acids may be obtained if the oxidation is carried out under suitably controlled conditions:¹²¹



Dimethylacrylic ester treated with fuming nitric acid gives α -nitrodimethylacrylic ester, $(\text{CH}_3)_2\text{C} = \text{C}(\text{NO}_2)\text{COOC}_2\text{H}_5$; this is converted to the isomeric nitro ester, $\text{CH}_3\text{C}(\text{:CH}_2)\text{CH}(\text{NO}_2)\text{COOC}_2\text{H}_5$, on treatment with alcoholic potassium hydroxide.

Ozone reacts normally with olefin carboxylic acids giving ozonides which may be decomposed by the usual methods to aldehydes and aldehyde acids:¹²²

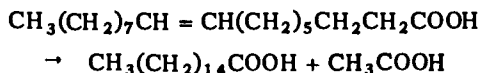


Olefin carboxylic acids react normally with perbenzoic acid forming oxido acids.¹²³

The lower unsaturated acids are readily reduced to the corresponding saturated acids by treatment with zinc and dilute sulfuric acid, while the higher olefinic acids are not affected by this treatment. Apparently only α,β -unsaturated acids are reduced by sodium amalgam.¹²⁴ All unsaturated acids are reduced by treatment with hydriodic acid and red phosphorus, and by catalytic hydrogenation in the presence of finely divided nickel, platinum, or palladium.¹²⁵

Some olefin carboxylic acids may be decarboxylated by heating their salts with sodium ethoxide;¹²⁶ thus, decylene is obtained in 50% yield by heating the barium salt of undecylenic acid with sodium ethoxide.¹²⁷ Decarboxylation is not brought about, however, when the sodium salts of the unsaturated acids are heated with soda lime. Some olefin dicarboxylic acids are decarboxylated on heating their sodium salts with aqueous alkali, although this treatment more often simply results in the isomerization of the acid.¹²⁸ Unsaturated β -hydroxy acids are readily decarboxylated and simultaneously dehydrated. An example is the formation of alloocimene from the condensation product of methylheptadienone and α -bromopropionic acid in the presence of zinc.¹⁵⁵ The lower conjugated diolefinic acids are decarboxylated when heated with baryta water, but the resulting compounds are dimeric or trimeric hydrocarbons and not the expected butadienes.¹²⁹

Rupture of the carbon chain of unsaturated acids takes place when these acids are fused with alkalis, and results in the formation of two carboxylic acids. Methacrylic acid yields formic and propionic acids. It would appear that cleavage generally takes place between the α and β carbon atoms, irrespective of the position of the double bond.¹³⁰ Oleic acid, for example, gives palmitic and acetic acid, the reaction proceeding in a smooth manner:¹³¹



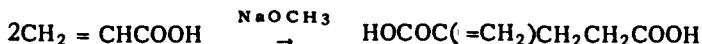
Many unsaturated acids undergo *isomerization* under the influence of various reagents. The fact has already been noted that the double bond in β,γ -unsaturated acids, and other acids in which the olefinic linkage is further removed from the carboxyl group, migrates toward the carboxyl group under the action of boiling caustic.

Fumaric acid is converted to maleic anhydride when treated with PCl_5 , POCl_3 or P_2O_5 .¹³² Maleic acid, in turn, may be converted to fumaric acid by various methods. Heating the ester with iodine, or the acid to 200° in a sealed tube accomplishes the result.¹³³ The transformation is also brought about by several reagents in the cold, such as aqueous hydrogen halides, sulfur dioxide, hydrogen sulfide, etc.¹³⁴ The conversion of the *cis* to *trans* form comes about on treating maleic acid amide or maleic acid anilide with alcoholic caustic.

Isocrotonic acid changes quantitatively into crotonic acid in a few minutes when a trace of bromine is added to its aqueous solution placed in the sunlight.¹³⁵

Oleic acid changes to its solid crystalline isomer, elaidic acid, when treated with a comparatively small quantity of concentrated nitric acid.

Esters of unsaturated acids, such as those of acrylic or crotonic acids, form dimers under the influence of sodium methoxide:¹³⁶



The lower conjugated diolefinic acids readily polymerize when heated. Methacrylic acid, $\text{CH}_2 = \text{C}(\text{CH}_3)\text{COOH}$, polymerizes on long standing or in contact with hydrogen chloride.¹³⁷ Itaconic esters polymerize to glass-like products when stored in an impure condition.¹³⁸

α,β -Unsaturated acids are of about the same strength as the corresponding saturated acids, but γ,δ -unsaturated acids are considerably stronger.

The velocity of esterification of α,β -unsaturated acids is lower than that of the corresponding saturated acids. The esterification of β,γ - and γ,δ -unsaturated acids proceeds at about the same rate as that of the saturated acids.¹³⁹

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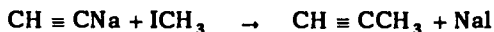
CHAPTER 19

ACETYLENIC COMPOUNDS.

ACETYLENIC HYDROCARBONS

Formation

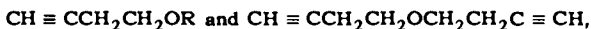
Many acetylenic hydrocarbons may be prepared from acetylene, through its alkali metal derivatives, by replacement of the metal with a hydrocarbon residue by reaction with an alkyl halide. Alkyl iodides react most readily. Reaction is best carried out in liquid ammonia:¹



Reactions of this type have served to introduce straight chain alkyl groups, alkyl groups branched beyond the 2-position, and arylated methyl groups into the molecule of acetylene or acetylenic compounds of the type $\text{RC} \equiv \text{CH}$.

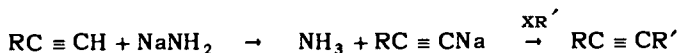
The reaction of alkyl halides with sodium acetylide is often strongly exothermic; for that reason the alkyl halide must be added slowly, or the reaction must be carried out at -50° . The reaction is generally complete within 3 to 4 hours. The yield of acetylenes with alkyl groups up to n-decyl ranges between 50 and 80%.⁵⁰¹ Yields may be improved with the less reactive halides by allowing the reaction to proceed first at room temperature under autogenic pressure, then heating at 50° .¹⁵⁶ The solubility of sodium derivatives of alkylacetylenes in liquid ammonia decreases with increase in the chain length, and synthesis of dialkyl derivatives with alkyl groups containing more than ten carbon atoms becomes difficult. Lithium derivatives of such long chain acetylenes serve well for the purpose.⁵⁰² Diacetylenes have been prepared by this method from α, ω -primary halides.⁵⁰³ Ethylene dibromide gives largely dehydrobromination products, and methylene dibromide gives penta-1,3-diyne in low yield.⁵⁰⁴ ω, ω' -Iodochlorides and -bromochlorides, reacting with one molecular equivalent of sodium acetylide yield ω -chloroalkylacetylenes.⁵⁰⁵ The requisite iodo chlorides may be prepared from ω, ω' -dichlorides by reaction with one molecular equivalent of sodium iodide in acetone solution.⁵⁰⁶

Alkyl halides and sulfates, as well as alkyl esters of aromatic sulfonic acids have been employed for the preparation of a wide range of mono and disubstituted acetylenes from the sodio derivatives of the acetylenic compounds in solution in liquid ammonia.² Vinylacetylene may be alkylated by this method.³ Acetylenic ethers, such as



can be obtained in good yield from bromo ethers and sodium acetylide.⁴

Dialkyl acetylenes may be prepared by first synthesizing a monoalkyl acetylene, converting this to its sodium derivative by the action of sodamide, and finally treating with an alkyl halide:⁵



The reaction may be carried out in one step by using two molecular equivalents of the halide to one of sodium acetylide and adding one molecular equivalent of sodamide to the mixture. Symmetrical dialkyl acetylenes may be obtained by causing lower alkyl halides to react with a mixture of sodium acetylide and sodamide in liquid ammonia.

Alkyl acetylenes entirely free from alkyl halides may be prepared by treating a liquid ammonia solution of sodium acetylide with an alkyl iodide in an autoclave, and allowing sufficient time for the conversion of unreacted alkyl iodide to alkyl ammonium iodide. In preparing methyl and ethyl acetylenes, the gaseous products evolved are passed successively through water or dilute sulfuric acid, a calcium chloride tube, and a refrigerated condenser. In preparing higher acetylenic homologs, water is cautiously added to the ammoniacal solution, whereby most of the acetylenic compound separates as an oil layer, which is drawn off, dried, and purified by distillation.

Alkali acetylides remove hydrogen halide from many organic halides, forming olefins. Dehydrohalogenation has been observed with secondary and tertiary halides, primary halides with a carbon chain at 2-position, vinyl halides and their homologs. Removal of hydrogen halide takes place also with compounds having two or more halogen atoms attached to the same, or to adjacent carbon atoms. A partial removal of hydrogen halide takes place from most straight chain alkyl halides.⁶

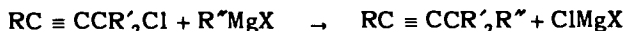
Isopropyl chloride and iodide, isobutyl, *sec*-butyl, *tert*-butyl, active amyl, *tert*-amyl, and *sec*-hexyl iodides react with sodium acetylides in solution in liquid ammonia at a moderately high temperature, and yield olefins as the principal product of the reaction.

The reaction of sodium acetylide with allyl halides, $\text{CH}_2 = \text{CHCH}_2\text{X}$, proceeds in a complex manner; the initial product of the reaction, allylacetylene, forms a sodium derivative, and further condensation leads to the formation of 8- and 11-carbon branched chain compounds.⁵⁰⁷ Halogenated ethylenes of the type $\text{RCH} = \text{CHCH}_2\text{CH}_2\text{X}$ yield exclusively the corresponding butadienes $\text{RCH} = \text{CHCH} = \text{CH}_2$ on reaction with sodium acetylide.⁵⁰⁸ 1,5-Alkynes $\text{RCH} = \text{CHCH}_2\text{CH}_2\text{C} \equiv \text{CH}$ may be obtained, however, through the reaction of the halides $\text{RCH} = \text{CHCH}_2\text{Br}$ with propargylmagnesium bromide.⁵⁰⁹ Haloethylenes $\text{RCH} = \text{CH}(\text{CH}_2)_n\text{Cl}$ with $n \geq 3$, react normally with sodium acetylide to form the corresponding alkenyne.⁵¹⁰

Many alkyl halides fail to react with sodium acetylides in liquid ammonia under atmospheric pressure, while at room temperature and under autogenic pressure amines are the predominant product in several instances. Amine formation takes place most readily with iodides, and least readily with chlorides.

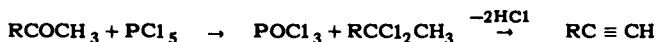
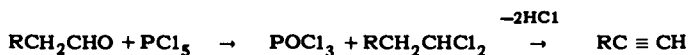
Substituted acetylenes may be prepared also through the reaction of organic halo compounds with acetylenic Grignard compounds.⁷ The latter react with only a limited number of halo compounds, notably with allyl and substituted propargyl halides, phenylated methyl halides, cyanogen halides, α -halo ethers, and acyl halides. The reaction of acetylenemagnesium bromide with allyl halides proceeds smoothly in the presence of small quantities of cuprous chloride or bromide to form 1-en-yne, though the yields tend to be low.⁵¹¹ The reagents react readily with alkyl sulfates and with esters of aromatic sulfonic acids.⁸

Acetylenic hydrocarbons may also be obtained from acetylenic halides by reaction with organomagnesium halides:



Homologs of acetylene may be prepared from monohalo olefins or dihalo addition products of olefins, by dehydrohalogenation by reaction with alcoholic potassium hydroxide.⁹ Excessive heating should be avoided when dehydrohalogenation is carried out with alcoholic caustic. Dehydrohalogenation may also be carried out by use of solid potassium hydroxide.

Allylene, $CH_3C \equiv CH$, has been obtained, through the dehydrochlorination of chloropropylene, $CH_3CCl = CH_2$, and *crotylene*, $CH_3C \equiv CCH_3$, from 2,3-dibromopropane, $CH_3CHBrCHBrCH_3$. An entire series of homologs of acetylene have been prepared from the bromides of higher olefins.¹⁰ Dichlorides derived from aldehydes and ketones by replacement of the carbonyl oxygen with two chlorine atoms also yield acetylenic hydrocarbons on treatment with alcoholic potassium hydroxide:¹¹



Bromides react more readily than chlorides. Heating in a sealed tube to a temperature in the neighborhood of 170° may be necessary with certain halides, but prolonged refluxing at atmospheric pressure is generally sufficient with arylchloro- or bromoethylenes. The use of concentrated solutions of caustic is desirable. The reaction time varies according to the nature of the halo compound. A few minutes heating at 100° with moderately concentrated caustic is sufficient to complete the reaction with some halides, while others may require refluxing with concentrated caustic for several hours. The use of butyl alcoholic caustic may present advantages in some cases.¹² Cellosolve has been used successfully as a solvent for the dehydrochlorination of polyvinyl chloride.¹³ Pyridine has also been employed as a solvent.¹⁴ Aqueous alkali is to be preferred for the dehydrohalogenation of certain halo acids.¹⁴

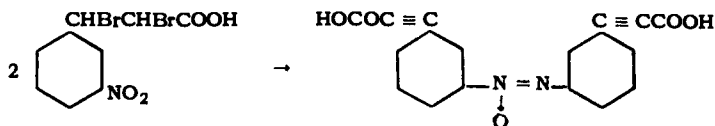
Dehydrohalogenation may be effectively carried out by distillation under reduced pressure over *solid potassium hydroxide*. The method has been applied successfully to the preparation of sensitive acetylenic ethers.¹⁵ Molten potassium hydroxide has also been employed for the dehydrohalogenation of halo compounds to substituted acetylenes. Phenylacetylene may be obtained, for example, by dropping ω -bromostyrene into molten potassium hydroxide heated to 200 – 220° .¹⁶

Treatment with alcoholic potassium hydroxide at the higher temperatures required for the dehydrohalogenation of aliphatic halides often brings about a shift of the triple bond toward the center of the molecule.

Substituted cinnamic acid dibromides or their esters are readily converted to phenylpropionic acids on treatment with caustic,¹⁷ but the reaction is usually accompanied by some decarboxylation. This side reaction may be greatly reduced by carrying out the treatment with caustic at a low temperature, and by avoiding any undue rise in temperature during the final acidification of the alkaline solution. Since decarboxylation of such acetylenic acids occurs readily, many substituted phenylacetylenes have been prepared by this route.¹⁸

Aliphatic acids with a triple bond adjacent to the carboxyl group cannot be prepared from dibromides of the corresponding olefinic acids or from α -halo olefinic acids.

Cis- α -bromo-*m*-nitrocinnamic acid, or *m*-nitrocinnamic acid dibromide, treated with alcoholic potassium hydroxide, is converted to *m*-azoxyphenylpropionic acid:^{14,19}



Dehydrohalogenation of organic halo compounds to acetylenic compounds has been brought about in some cases by use of ethanolic *sodium ethoxide*. Tolans are readily formed, for example, when stilbene dibromides are heated with this reagent. In this reaction, replacement of the halogen with an alkoxy group also takes place.

Diaryl acetylenes may also be obtained by heating unsymmetrical diaryl haloethylenes. Diaryl acetylenes have been prepared through the reaction of diaryl haloethylenes with potassium- or sodium amide in liquid ammonia.

Asym-diphenyl- or ditolyldichloroethylenes give mainly diphenyl or ditolyl acetic acid on treatment with ethanolic sodium ethoxide, whereas di-*p*-anilyl- and di-*p*-phenetyldichloroethylenes give the corresponding tolans in 80% yield by the same treatment.¹⁹

Treatment of *o*- and *p*-nitrobenzal chlorides with ethanolic sodium ethoxide results in the formation of *o,o'*- and *p,p'*-dinitrotolans,²⁰ the *ortho* compound forming in 36-39% yield. An acetal results when *m*-nitrobenzal chloride is similarly treated.

Dehydrohalogenation may be accomplished quite satisfactorily by use of sodamide.²¹ The acetylenic compound is formed as a solid complex of an unknown nature with sodamide. The reaction is applicable to compounds of the type $\text{RCHX-CH}_2\text{X}$, RCH_2CHX_2 , RCX_2CH_3 , $\text{RCX}=\text{CH}_2$, and $\text{RCH}=\text{CHX}$. Vinylacetylene has been obtained by this method from the readily available 1,4-dichlorobut-2-ene.⁵¹²

The halide is added dropwise to an excess of the finely pulverized amide in an inert liquid heated to 150-160°. The reaction is complete when ammonia ceases to be evolved or is evolved very slowly. The reaction is often complete within 15 minutes. A petroleum fraction boiling above 250° serves satisfactorily as the liquid medium. The substituted acetylene is obtained in the form of a complex with the excess amide, which is isolated and decomposed with dilute hydrochloric acid or with acetic acid.²² The yields generally range between 60 and 85% of the theoretically expected quantity. When a small amount of aniline is used in conjunction with sodamide, dehydrohalogenation of compounds such as bromostyrene is facilitated to such an extent that the reaction may be carried out in ether at ordinary temperature.²³

The quality of the amide used is of importance for the success of the method. The reagent is partially deactivated on exposure to atmospheric moisture, through the formation of a coating of sodium hydroxide on the particles of the amide. A yellow color often develops in old samples of amide which have been exposed to air, due to the formation of peroxide; this compound is dangerously explosive and samples contaminated with it should be destroyed at once.²⁴ A highly reactive form of sodamide may be prepared by causing sodium to react with liquid ammonia in the presence of sodium oxide and salts of iron, nickel, or cobalt soluble in ammonia.²⁵ By adding the solution of the amide to a mineral oil at room temperature and heating to drive off the ammonia, a reactive, finely divided suspension of the amide is obtained.

Sodium amide reacts with excessive vigor with substituted α -chlorostyrenes, and the use of alcoholic alkali is to be preferred with these compounds.²⁶ The

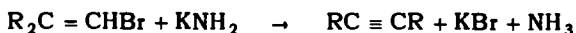
method is applicable to the synthesis of 3-aryl-1-propynes, but the final hydrolysis of the reaction mixture should be effected with great care, because of the ready tendency of these acetylene derivatives toward rearrangement.

Sodium amide brings about the conversion of disubstituted acetylenes and allenes into monosubstituted acetylenes through molecular rearrangement. The transformation proceeds rapidly at 150 to 160°, although dehydrohalogenation of the halo olefin may often be carried out with only partial isomerization of the resulting acetylene.

Repeated methylation followed by isomerization under the influence of sodium amide makes possible the preparation of otherwise relatively inaccessible monosubstituted acetylenes.

Removal of adjacent halogens with the formation of olefins is an important side reaction when dibromides are treated with sodium amide.

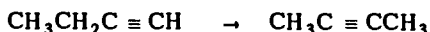
Tolans are formed readily from *asym*-diaryl halo ethylenes on treatment with potassium- or sodium amide in ammoniacal solution:²⁷



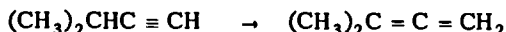
High yields of the tolans are obtained if R is phenyl, tolyl, methoxyphenyl, 3,4-dimethylphenyl, and xenyl; but yields of 50 to 70% are obtained when R is a phenyl group with an ethyl, propyl, or butyl group in the *para* position. The position of attachment in the benzene ring is not changed during the migration. This reaction probably offers the best method for the preparation of tolans, since diaryl bromoethylenes are easily prepared from unsymmetrical diaryl ethanes which are in turn obtainable from the readily accessible diaryl methyl carbinols.

Dehydrohalogenation to acetylenic compounds has been effected by passing the vapors of the halo compound over calcium oxide at red heat.²⁸ *Dichloroacetylene* is best prepared by passing trichloroethylene over a mixture of potassium hydroxide and calcium hydroxide at 130°.²⁹

Certain disubstituted acetylenes result through the isomerization of monosubstituted acetylenes by a shift of the position of the triple bond:³⁰

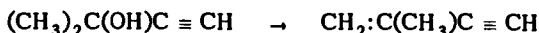


Hydrocarbons with a secondary alkyl group are converted to allenes,



while hydrocarbons with a tertiary carbon, such as $(CH_3)_2CC \equiv CH$, do not undergo any change.

Vinylacetylenes have been prepared through the dehydration of the readily accessible tertiary acetylenic carbinols:

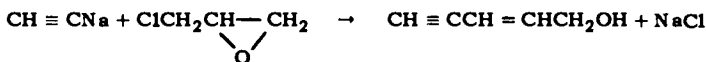


Dehydration may be brought about by a variety of agents, including acetic anhydride containing a little sulfuric acid, phosphoric acid, sulfuric acid, etc.³¹ Dehydration has also been accomplished by passing the vapors of the acetylenic carbinol over heated magnesium sulfate or aluminum oxide.³²

Substitution and debromination take place simultaneously when 1,2,3-tribromoprop-1-ene is made to react with phenylmagnesium bromide, debromination involving the formation of diphenyl and benzylacetylene:⁵¹³

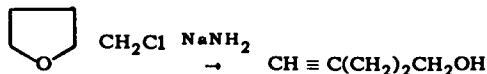


The reaction of sodium acetylide with epichlorhydrin in liquid ammonia results in the replacement of the halogen with the acetylenic group as well as the appearance of an unsaturated bond:⁵¹⁴

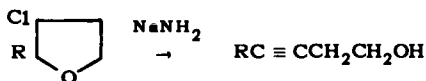


The pent-2-en-4-yn-1-ol is obtained in 45% yield. Homologs of epichlorhydrin react in a similar manner, although the yields of unsaturated alcohols are low, generally in the order of 20%.

A similar type of oxygen bridge rupture resulting in the appearance of an unsaturated bond is observed in the dehydrohalogenation of tetrahydrofurfuryl chloride with sodamide in liquid ammonia, which results in the formation of a γ -hydroxyacetylene in 85% yield:

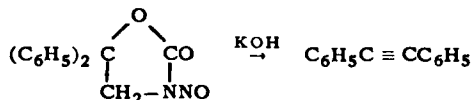


The same effect is observed in the dehydrohalogenation of 1-alkyl-2-chlorotetrahydrofurans with sodamide in liquid ammonia.⁵¹⁵



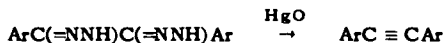
The ethyl substituted derivative is obtained in 30% yield.

The action of alkalis on aromatic 3-nitroso-2-oxazolidones results in the formation of tolans, the reaction involving the migration of an aryl group, as observed with asymmetrical diarylhaloethylenes above, and a rupture of an oxygen bridge, bringing about the appearance of an unsaturated bond:⁵¹⁶



The method has been employed for the preparation of labeled diphenylacetylene.⁵¹⁷

Tolans result when dihydrazones of benzils are heated with yellow mercuric oxide:⁵¹⁸



The method is applicable to aliphatic and cycloaliphatic vicinal dihydrazones, and cyclic acetylenic compounds have been prepared by its use.⁵¹⁹ It has been demonstrated that the lower steric limit of cycloalkynes is reached with cyclooctyne.

Diacetylenes are obtained through the oxidation of the copper compound of monosubstituted acetylenes:



Oxidation may be carried out by atmospheric oxygen or by use of various oxidizing agents such as potassium ferricyanide, cupric chloride and bromide.³³ In

general, a reaction expected to yield a cupric acetylide invariably gives a diacetylene. Diphenyldiacetylene, $C_6H_5C \equiv CC \equiv CC_6H_5$, is formed when steam is passed through a solution of copper phenylacetylide, $C_6H_5C \equiv CCu$ in pyridine.³⁴⁴

The coupling of hex-4-en-1-yn-3-ol may be mentioned as illustrative of the procedure followed. A solution of 80 gm of ammonium chloride and 50 gm of commercial cuprous chloride in 200 cc of water is brought to pH 6.5 by the addition of aqua ammonia of density 0.88. Usually 25 cc of the latter are required for the purpose. Nineteen and two-tenths gram of the acetylenic compound are now added and the mixture is shaken in a closed container while oxygen is led into it until uptake of oxygen ceases. The green suspension which forms is extracted with six 100 cc portions of ether, the combined extracts are dried, the ether is evaporated off and the residue is heated to 50° under 0.1 mm pressure in order to remove the unreacted carbinol. The product is then purified by crystallization from benzene. The yield is 17.6 gm or 98% of the theoretically expected quantity.⁵²⁰

Diacetylenes are obtained also through the oxidation of acetylenic Grignard reagents by atmospheric oxygen, iodine, cupric bromide, and certain other oxidizing agents:³⁴



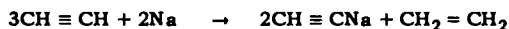
This method is not satisfactory for the preparation of *diacetylene* itself.³⁵ This compound may be obtained in the form of the copper salt by heating diacetylene dicarboxylic acid, $HOCOC \equiv C - C \equiv CCOOH$, with an ammoniacal solution of copper chloride. The free hydrocarbon results on heating the copper derivative with aqueous potassium cyanide.³⁶

Diacetylenes may be obtained through the reaction of acetylenic Grignard compounds with primary acetylenic halo compounds:³⁷



Metallic Derivatives of Acetylene

Acetylene gives two series of metallic derivatives with alkali metals, $CH \equiv CM$ and $MC \equiv CM$. Mono sodium acetylide may be prepared by passing acetylene into a solution of sodium in liquid ammonia under atmospheric pressure:



The reaction proceeds slowly because of poor contact between the solution and acetylene due to the continuous boiling of the liquid. The difficulty is largely avoided by using solid carbon dioxide as a cooling medium.³⁸ The quality of the product is improved and the rate of its formation is increased when the sodium is added at such a rate that no substantial excess of the metal is present in solution at any time.³⁹ The use of sodium amide in liquid ammoniacal solution is to be preferred to the use of metallic sodium.⁴⁰ The acetylene is passed at the rate of 2 to 3 lit per hour through a stirred suspension of sodamide in liquid ammonia cooled to -35° , until the gray mixture becomes uniformly black; this requires about one hour. The acetylene is purified by passage first through a trap cooled with a solid carbon dioxide-acetone mixture, then through two concentrated sulfuric acid wash bottles.

A reactive form of sodium acetylide is obtained by passing acetylene into a suspension of sodium naphthalene in dimethyl ether.⁴¹

Monosodium acetylide results when acetylene is conducted over metallic sodium heated to 200°. At higher temperatures the disodium derivative is formed.⁴²

Lithium, potassium, and sodium acetylides may be prepared through the reaction of the amides of these metals with acetylene.⁴⁹⁰

Lithium alkylacetylides, $\text{AlkC} \equiv \text{CLi}$, may be prepared through the reaction of metallic lithium with the corresponding mercury alkylacetylide in dioxane solution.

Acetylenic compounds $\text{RC} \equiv \text{CH}$ react with cuprous salts in ammoniacal solution to form the insoluble cuprous acetylides $\text{RC} \equiv \text{CCu}$. These compounds are decomposed by dilute acids or with aqueous sodium cyanide to the free ethynyl compound, $\text{RC} \equiv \text{CH}$ and a cuprous salt.

Acetylene and monosubstituted acetylenes react with ethylmagnesium bromide to form acetylenic magnesium compounds.

The copper derivative of acetylene, C_2Cu_2 , is precipitated as a brownish red amorphous solid when acetylene is conducted into an ammoniacal solution of cuprous chloride.⁴³ Silver acetylide results similarly when acetylene is led into an ammoniacal solution of a silver salt.⁴⁴

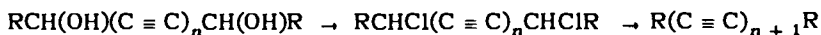
Mercury acetylide results as a white precipitate when a current of acetylene is passed into an alkaline mercuric iodide-potassium iodide solution.⁴⁵

Sodium reacts in the cold with monosubstituted acetylenes, $\text{RC} \equiv \text{CH}$, in solution in ether to form their sodium derivatives, $\text{RC} \equiv \text{CNa}$.⁴⁶ These homologs of acetylene also react with ammoniacal solutions of cuprous chloride and silver nitrate to form precipitates of the copper and silver salts. The higher homologs react with silver nitrate in alcoholic solution to form the silver acetylide.⁴⁷

Acetylenedimagnesium bromide, $\text{BrMgC} \equiv \text{CMgBr}$, is formed as a finely divided precipitate when acetylene is led into a benzene solution of ethylmagnesium bromide.⁵²¹

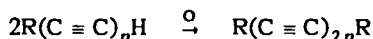
Polyyne⁴⁸⁵

Two principal routes have been developed for the synthesis of polyyne. In one, acetylenic glycols, $\text{RCH(OH)(C} \equiv \text{C)}_n\text{CH(OH)R}$, are converted to the corresponding dichloro derivatives by treatment with thionyl chloride in the presence of pyridine. The dichlorides formed are then dehydrochlorinated by treatment with sodamide in liquid ammonia:⁴⁹¹



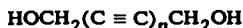
Acetylenic dichlorides, $\text{ClCH}_2(\text{C} \equiv \text{C)}_n\text{CH}_2\text{Cl}$, yield the monosodium derivative, $\text{Na(C} \equiv \text{C)}_{n+1}\text{H}$, by this treatment. The glycols may be obtained through the reaction of acetylenic compounds $\text{HC} \equiv \text{C(C} \equiv \text{C)}_{n-2}\text{C} \equiv \text{CH}$ with aldehydes in the presence of sodium ethoxide or various other condensing agents.

The second route consists in the oxidation of a monosubstituted polyyne with oxygen in the presence of cuprous and ammonium chlorides:



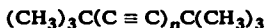
Best results are obtained in the preparation of diacetylene by adjusting the pH value to 3, assuring intimate contact with oxygen by good agitation, and using a 4 to 6 molal proportion of cuprous chloride.⁴⁹² Acetylenes of widely varying type have been successfully submitted to the reaction. Coupling may be effected also by the action of cupric bromide or iodine on the Grignard derivative of the monosubstituted acetylene.

Compounds $\text{H}(\text{C} \equiv \text{C})_n\text{H}$ condensing with formaldehyde yield the diols



which by conversion to the corresponding dichloride and dehydrohalogenation, give the next higher polyne, $\text{H}(\text{C} \equiv \text{C})_{n+1}\text{H}$. Polyynes of this type with up to five acetylenic groups have been prepared by this route; those with a larger number of acetylene groups cannot be obtained by this method because of the instability of the intermediate dichlorides.

The substituted polyynes $\text{R}(\text{C} \equiv \text{C})_{2n}\text{R}$ have been prepared by the oxidative coupling of monosubstituted polyynes $\text{R}(\text{C} \equiv \text{C})_n\text{H}$, which are obtained through the reaction of RCI with the monosodium polyacetylides $\text{H}(\text{C} \equiv \text{C})_n\text{Na}$. The longest chain obtainable by this method contains six acetylenic groups. Di-*tert*-butylacetylenes



are comparatively stable, and compounds of this type with up to seven acetylenic groups have been prepared. The triacetylenic body has been prepared from trimethylacetaldehyde and sodium diacetylide. The tetraacetylenic compound has been obtained by oxidative coupling from *tert*-butyldiacetylene, $(\text{CH}_3)_3\text{CC} \equiv \text{CC} \equiv \text{CH}$, which was prepared from trimethylacetaldehyde and the Grignard derivative of propargyl alcohol. The derivative with five acetylenic groups was prepared from the Grignard derivative of diacetylene and *tert*-butylpropargyl aldehyde $(\text{CH}_3)_3\text{CC} \equiv \text{CCHO}$, which was obtained through the reaction of *tert*-butylacetylenemagnesium bromide and orthoformic ester and hydrolysis of the resulting acetal. The hexaacetylenic compound was obtained through oxidative coupling from *tert*-butyltriacetylene, which was prepared from *tert*-butylpropargyl aldehyde and the Grignard compound derived from propargyl alcohol. The derivative with seven acetylenic groups was prepared from the Grignard compound derived from diacetylene and *tert*-butyldiacetylenic aldehyde, $(\text{CH}_3)_3\text{C}(\text{C} \equiv \text{C})_2\text{CHO}$, which was in turn prepared through the reaction of *tert*-butyldiacetylene and formic ester.

sym-Phenylpolyynes $\text{C}_6\text{H}_5(\text{C} \equiv \text{C})_n\text{C}_6\text{H}_5$ have been prepared by similar methods.⁵² These compounds are also comparatively stable, and a representative with eight acetylenic group is known.⁵²³ This was obtained through the oxidative coupling of phenyltetraacetylene, $\text{C}_6\text{H}_5(\text{C} \equiv \text{C})_4\text{H}$, which was prepared from bromocinnamaldehyde and pentanediyne-ol.

Reactions of Acetylenic Compounds

Acetylene and its derivatives undergo additive reactions common to unsaturated compounds. Addition may take place in two stages, the first resulting in the formation of an olefinic compound, the second stage yielding a saturated derivative. These reactions are similar to those of olefinic compounds. There are, however, distinct differences between the behavior of acetylenic compounds and the olefins. In particular, the ready hydration of acetylenic compounds under the influence of certain catalysts is not paralleled in the ethylenic series. In general, addition reactions take place more readily in the acetylenic series than with olefinic compounds.

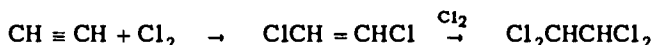
Halogenation

Chlorine and bromine react readily with acetylene and its homologs. Chlorine does not react readily with acetylene in the dark and at ordinary temperature and pressure, even though the reaction is highly exothermic and is accelerated

by heat. Once initiated, the reaction may proceed with explosive violence with the formation of much carbon and hydrogen chloride, together with other products. Acetylene ignites automatically when conducted into a cold saturated solution of chlorine in water.

Reaction proceeds smoothly when a mixture of acetylene with not more than 10% chlorine is heated, and results in the formation of dichloroethylene, ClCH:CHCl . Acetylene tetrachloride is formed when chlorine is led into a solution of acetylene in acetylene tetrachloride containing a catalyst such as iron. This reaction is also induced by radiation. Acetylene tetrachloride is formed when acetylene is chlorinated in the presence of antimony pentachloride^(*),⁴⁶

At moderate temperatures chlorine apparently adds in successive stages to acetylene, forming first dichloroethylene and then tetrachloroethane:



At temperatures in excess of 100° and in the absence of catalysts, hexachloroethane appears to be the principal product.⁴⁸

In the commercial chlorination of acetylene, iron and iron compounds are used as catalysts.⁴⁹ The catalyst may be employed in suspension in a chlorinated hydrocarbon such as tetrachloroethane, through which is passed acetylene. It may also be charged in a tower down which runs the solution of acetylene to be chlorinated. Tetrachloroethane is obtained as the principal product in 90% yield when the reaction is conducted at $60\text{--}75^\circ$. Chlorination has been carried out successfully at elevated temperature by use of copper or calcium chloride as catalyst and diluting the acetylene with superheated steam.⁵⁰

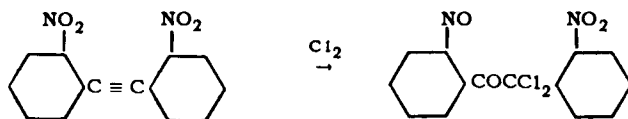
Tetrachloroethane is also made commercially by passing chlorine and acetylene simultaneously into a mixture of antimony pentachloride and tetrachloroethane. Intimate contact of the gases is assured by good agitation, and the mixture is kept cool by cold water circulating through lead coils.

Trichloroethylene is obtained by removing a molecule of hydrogen chloride from tetrachloroethane by treatment with an alkaline reagent, such as sodium hydroxide, sodium carbonate, lime, etc. Pentachloroethane is formed from trichloroethylene by the addition of chlorine. Dichloroacetylene, $\text{ClC} \equiv \text{CCl}$ is formed by removal of two molecules of hydrogen chloride from tetrachloroethane by reaction with a suspension of potassium hydroxide in xylene at 80° . The gas is spontaneously inflammable in air.

The reaction of an excess of chlorine with acetylene at high temperatures leads to the formation of hexachlorobutadiene.⁵¹

Only two halogen atoms add to acetylenic triple bonds if a carboxyl group is attached to one of the acetylenic carbon atoms.³⁴⁵

A nitroso nitro dichloro ketone results through the chlorination of O, O' -dinitrotolane:³⁴⁶



Liquid bromine, or bromine in solution in an inert solvent, adds smoothly to

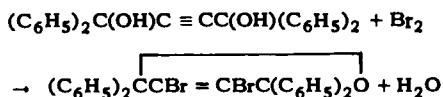
(*) Acetylene forms a crystalline addition compound with antimony pentachloride, which decomposes to dichloroethylene and antimony trichloride when heated.

acetylene, presumably first forming the dibromo derivative and finally giving the tetrabromo compound in yields ranging 90 to 95% of theory.⁵²

In the vapor-phase bromination of acetylene at 150°, the dibromide is first formed; further addition of bromine takes place more slowly and only when an excess of the halogen is present.

Bromination of *p*-bromophenylpropionic acid in aqueous or dilute sodium carbonate solution resulted in the formation of *p*-bromophenylbromoacetylene, $\text{BrC}_6\text{H}_4\text{C} \equiv \text{CBr}$.³⁴⁷

Tetraphenylbutynediol adds two atoms of bromine and gives tetraphenyldibromofuran in 90% yield by elimination of the elements of water:³⁴⁸



Tetraphenylbutynediol yields a mixture of an open chain bromo derivative and bromofuran, while biphenylbutynediol gives largely a brominated open chain derivative.

Iodine reacts with acetylene much less readily than either bromine or chlorine, giving a diiodide. Reaction takes place on heating in a sealed tube at 100° for several hours.⁵³ Direct iodination of acetylenic compounds is possible at -34° in liquid ammonia.³⁴⁹ Iodinated compounds are obtained in quantitative yield by this method from aryl and vinyl substituted acetylenes, but reaction with ethyl-, butyl- and amylacetylene is slow and the yields are low.

Simultaneous addition and substitution with iodine takes place when acetylene in the nascent condition is made to react with iodine in benzene solution.⁴⁸⁷ Propionic acid gives diiodoacrylic acid, $\text{ICH} = \text{CICOOH}$, when heated with iodine for 6 hours.⁴⁸⁸ The addition of iodine to phenylpropionic acid is catalyzed with ferrous iodide.⁴⁸⁹

The normal addition of chlorine or bromine to substituted acetylenes leads to the formation of dihalo derivatives which may be generally halogenated further to the tetrahalo compound. The groups R in substituted acetylenes $\text{RC} \equiv \text{CR}'$ influence the course of the reaction with halogens. Tolan, for example, gives only a dibromo compound,⁵⁴ and α,β -acetylenic acids generally give only dihalo derivatives.⁵⁵

Haloacetylenes

The reaction of halogens with metallic acetylides results in the formation of haloacetylenes:



Mono sodium acetylide may be converted to the dihalo compound by reaction with a halogen in the presence of some alkali or other compounds capable of combining with the generated halogen acid:

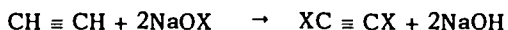


The reaction with the monosodium compound, leading to the formation of the iodide, may also be carried out successfully in liquid ammonia.⁵⁶ Iodopropionic ester, $\text{IC} \equiv \text{CCOOC}_2\text{H}_5$, has been obtained by the reaction of iodine in

aqueous potassium iodide solution with the moist copper compound of propiolic ester.⁴⁶¹ The chloro and bromo compounds are poisonous, explosive, and spontaneously inflammable gases.

Alkyl acetylene chlorides, $RC \equiv CCl$, result through the reaction of the potassium derivative of the alkyl acetylene with chlorine at -70° .⁵⁷

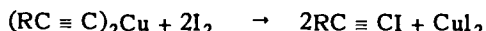
Haloacetylenes are formed also through the reaction of alkaline hypohalites with acetylene:⁵⁸



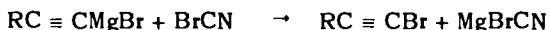
An alkaline solution is used for the purpose, containing at least four moles of free alkali in 0.5 to 0.7 normal hypohalite solution. Hypiodites react instantly, while hypobromites and hypochlorites react less readily. Dichloroacetylene has been made by this reaction,⁵⁹ although the compound is obtained more conveniently by passing a mixture of trichloroethylene and ether over alkalies heated to 130° , when a stable, 1:1 molecular complex of the dichloroacetylene and ether is formed.⁶⁰

Halides of monosubstituted acetylenes $RC \equiv CH$ may also be prepared through the reaction of the acetylene with a hypohalite. Iodopropiolic acid has been prepared by this method from propiolic acid, the compound giving monoiodoacetylene on decarboxylation.⁶¹ The hydrogen in such compounds is replaced with a halogen most readily when the acetylenic bond is conjugated with a benzenoid nucleus or an ethylenic linkage.

Haloacetylenes may also be obtained through the reaction of halogens with acetylene magnesium halides, the bromo compound being obtained by reaction in ethereal solution at -32° . The diiodide is readily obtained through the reaction of iodine at 0° with acetylenedimagnesium bromide in ethereal solution.⁶² Monosubstituted acetylenic iodides are obtained also through the reaction of iodine with heavy metal derivatives of monosubstituted acetylenic bodies:



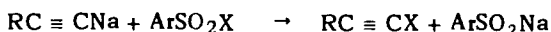
Acetylenic bromides or iodides may be obtained in 60-80% yield through the reaction of cyanogen bromide or iodide with halomagnesium acetylides:⁶³



Reaction with cyanogen chloride leads to the formation of acetylenic nitriles in good yield.

Bromoacetylene burns with great evolution of heat when brought into contact with air; in the presence of only a limited supply of air the compound burns slowly with evolution of fumes and without carbon formation. When diluted with a large volume of air, it does not burn.

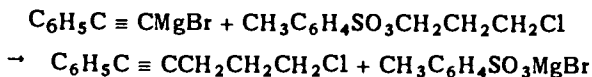
A method of wide applicability makes use of the reaction of alkali metal acetylides with aromatic sulfonyl halides:⁶⁴



The halo compounds are obtained in yields ranging 50 to 70% by this reaction.

Acetylenic Grignard compounds give acetylenic halides in poor yields by reaction with sulfonyl halides.

Acetylenic halides have been obtained by the reaction of acetylenic Grignard compounds with haloalkyl toluene sulfonates:⁶⁵



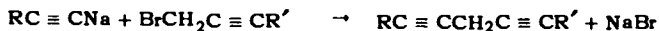
The yields of the halides range between 46 and 75% of theoretical.

The dichloro and dibromo compounds of acetylene take fire in contact with air, and may explode in the presence of traces of oxygen. The diiodo compound is more stable. Monochloro and monobromo derivatives of acetylene are highly unstable. The monoiodo compound is unknown.

Haloacetylenes, $\text{RC} \equiv \text{CX}$, behave in an exceptional manner. The halogen in these compounds exhibits a "positive" character; it is very unreactive, and attempts at new syntheses with compounds of this type have met with failure almost invariably.³⁵⁰

Grignard reagents react with acetylenic halo compounds in general to form halomagnesium derivatives of the acetylenic body. The reaction may follow a different course in the presence of metallic halides, such as cobalt chloride: Phenylacetylene bromide, $\text{C}_6\text{H}_5\text{C} \equiv \text{CBr}$, for example, reacting with methylmagnesium bromide in the presence of cobalt chloride, gives phenylmethylacetylene, $\text{C}_6\text{H}_5\text{C} \equiv \text{CCH}_3$, in 62% yield. Only iodoacetylenes react with magnesium to form Grignard derivatives.

β -Acetylenic bromides do not react with acetylenic magnesium compounds, but reaction takes place with the sodio derivative of acetylenic compounds:



The yields are usually in the neighborhood of 20%.

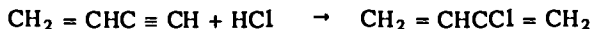
α -Bromoacetylenes may be prepared from α -hydroxyacetylenes by treatment with phosphorus tribromide in the presence of pyridine.⁵²⁴ β -Haloacetylenes may be obtained in high yield through the reaction of *p*-toluenesulfonates of *p*-hydroxyacetylenes with halides of lithium, calcium or sodium.⁵²⁵ β -Haloacetylenes do not undergo nucleophilic replacement of the halogen, but undergo dehydrohalogenation under the action of the reagents employed for such replacement. The halogen in γ -haloacetylenes, on the other hand, readily undergoes exchange with nucleophilic groups.

Reaction with Acids

The addition of *hydrogen halides* to acetylene and acetylenic hydrocarbons takes place slowly in the absence of catalysts. Vinyl halides have been prepared by heating acetylene with hydrogen halides at 100-120° under one to two atmospheres pressure for six hours. Reaction takes place readily in the presence of mercuric chloride⁶⁶ or cuprous chloride.⁶⁷ The reaction has been carried out by heating a mixture of acetylene and the hydrogen halide at 120-350° in contact with metallic catalysts supported on carbon or silica gel.⁶⁸ A carbon catalyst preheated at 200-600° with a hydrogen halide has also been used.⁶⁹

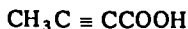
The principal product is ethylidene dichloride when two equivalents of hydrogen chloride are added to acetylene in the presence of mercuric chloride supported on silica gel.⁷⁰

Vinylacetylene reacting with hydrogen chloride in the presence of cuprous and ammonium chlorides gives chlorprene:⁷¹



Addition takes place in accordance with Markownikow's rule, although a peroxide effect is observed with hydrogen bromide.

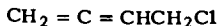
With true acetylenic bodies, the halogen never occupies a position at the end of a chain, when addition takes place in the normal manner. The possibility of the formation of two isomers is not excluded with asymmetric disubstituted compounds in the first stage of the reaction. Addition of a second hydrogen halide yields the dihalo compound with both halogens attached to the same carbon atom. Abnormal addition takes place with hydrogen bromide in the presence of perbenzoic acid, ascaridol and other organic peroxides.³⁵¹ *Trans* addition generally predominates.³⁵² The *cis* isomer is the primary product of addition with acetylenic acids, but may change to the *trans* isomer under the conditions of the reaction. Thus, pure *trans* bromofumaric acid is obtained from acetylenedicarboxylic acid. The solvent may exert a pronounced effect on the type of compound obtained; for example, phenylpropionic acid gives *cis* bromocinnamic acid in aqueous solution, and the *trans* isomer in bromobenzene; the *cis* acid is formed in nitroethane or nitromethane, but the compound rapidly changes to the *trans* isomer.³⁵³ The behavior of tetrolic acid



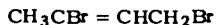
parallels that of phenylpropionic acid.³⁵³

Vinyl chloride may be prepared through the reaction of hydrogen chloride with acetylene at 180° in the presence of metallic chlorides.³⁵⁵ The reaction proceeds at room temperature in the presence of mercuric chloride or silica gel.³⁵⁶ Satisfactory results have been obtained with mixtures of salts such as one of the chlorides of barium and bismuth.

Addition of hydrogen chloride to vinylacetylene takes place on bubbling the gas through an aqueous solution of vinylacetylene containing 20 to 30% hydrogen chloride, 2 to 25% of cuprous chloride and variable quantities of ammonium chloride. The product obtained is 2-chloro-1,3-butadiene (chlorprene). The intermediate



has been obtained under milder conditions.³⁵⁷ The chlorobutadiene apparently is formed through the isomerization of this intermediate. In the reaction with hydrogen bromide, it is difficult to stop at the isoprene stage, but a 1,4-addition of a second molecule of the halogen acid takes place rapidly, giving 1,3-dibromobutene,



Halogen acids also react additively with divinylacetylene, hydrogen chloride, for example, giving 1,3-dichloro-2,4-hexadiene, $\text{ClCH}_2\text{CH} = \text{CClCH} = \text{CHCH}_3$.³⁵⁸

Vinyl ethers have been obtained through the reaction of vinyl chloride in alcoholic solution with sodium alkoxides at 80 to 100°. ⁴⁸⁴ The reaction is stated to be ap-

pliable to mono- and polyhydroxy alcohols as well as hydroaromatic and aromatic alcohols, mono and polyhydroxy phenols, cresols and naphthols.

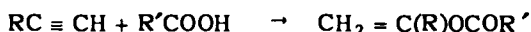
The addition of two equivalents of hydrogen bromide to acetylene in the presence of mercuric bromide gives a mixture of halogenated compounds containing 80 to 90% of ethylidene dibromide.⁷² Ethylene dibromide, $\text{BrCH}_2\text{CH}_2\text{Br}$, is formed in the presence of gaseous oxidizing agents.⁴⁸¹

The reaction of hydriodic acid with dibromoacetylene results in the formation of the dibromiodoethylene, $\text{Br}_2\text{C} = \text{CHI}$.

Hydrogen fluoride may be added to acetylene in the presence of mercuric oxide supported on active carbon.⁷³ With 1-alkynes 2,2-difluoro compounds are obtained, addition taking place in accordance with Markownikow's rule.⁷⁴

Combination of acetylene with concentrated sulfuric acid to vinyl sulfate has been brought about at 0 to -5° and under 2 to 5 atm pressure in the presence of mercuric sulfate.⁴⁸²

Carboxylic acids are capable of adding to the acetylenic bond in the presence of the boron trifluoride-mercuric oxide catalyst to form substituted vinyl esters as the first product:⁷⁵



Addition of a second molecule of acid results in the formation of the compound $\text{CH}_3\text{C(R)(OCOR}''\text{)}_2$, which decomposes to a ketone, CH_3COR , and the anhydride $(\text{R}'\text{CO})_2\text{O}$. The reaction can be stopped at the first stage under the proper conditions.

Combinations of mercuric salts with strong acids have also been used as catalysts. Mercuric sulfate with a small quantity of sulfuric acid has been used occasionally.⁷⁶ Mercuric oxide and sulfur trioxide or fuming sulfuric acid in acetic acid solution and a similar mixture containing acetylsulfuric acid appear to be also effective.

Vinyl acetate is prepared by passing a rapid current of acetylene through acetic acid containing a little mercuric sulfate in suspension. The temperature is maintained at 35° during the reaction. The catalyst is prepared by dissolving mercuric oxide in acetic acid, and adding sulfuric acid.

Thioacetic acid reacts vigorously with ethynyl compounds $\text{RC} \equiv \text{CH}$, especially in the presence of ascaridole, to give fair yields of the abnormal mono-adduct $\text{RCH} = \text{CHSCOCH}_3$. Treatment of these adducts with phenylhydrazine results in the formation of the phenylhydrazone of the aldehydes RCH_2CHO . Reaction of a second molecule of thioacetic acid with the first adduct results in an abnormal addition giving $\text{RCH(SCOCH}_3\text{)CH}_2\text{SCOCH}_3$, hydrolysis of which yields the dithiol $\text{RCH(SH)CH}_2\text{SH}$.⁵²⁶

α -Hydroxyisobutyric acid reacts with acetylene in the presence of mercuric salts to form an acetal-like compounds $\text{CH}_3\overbrace{\text{CHOC(CH}_3\text{)}_2\text{COO}}^{77}$.

Acetylene reacts with *hydrocyanic acid* in an aqueous solution containing cuprous chloride and ammonium chloride to form acrylonitrile.⁷⁸ Methylacetylene gives a mixture of methacrylonitrile, *cis*- and *trans*-crotononitrile, and some allyl cyanide.⁷⁹

β -Cyanoacrylic ester has been obtained through the reaction of hydrocyanic acid with propiolic ester in the presence of alkalis at room temperature or at a slightly elevated temperature, and under pressure.³⁵⁹

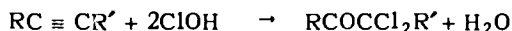
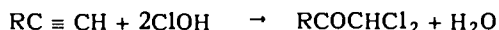
α,β -Dicyanoethylbenzene results from the reaction of potassium cyanide with methyl phenylpropiolate.³⁶⁰ The potassium derivative of α,β -dicyano- γ -phenylpropiolic methyl ester, $C_6H_5CH(CN)C(CN) = C(OK)OCH_3$, is apparently the intermediate formed in the reaction.

Vinylacetylene reacts with hydrocyanic acid in the presence of cuprous chloride forming 1-cyanobutadiene, $CH_2 = CHCH = CHCN$.⁸⁰

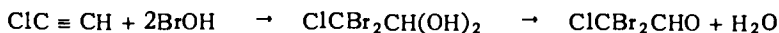
Hypochlorous acid reacting with acetylene gives dichloroacetaldehyde:



Special precautions must be observed to avoid an explosion.⁸¹ With substituted acetylenes α -dichloro ketones are formed:⁸²



Hypobromous acid gives a mixture of chloroacetyl bromide and chlorodibromoacetaldehyde with monochloroacetylene:



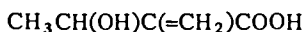
Reaction with Carbon Monoxide and Water

Acetylene is capable of reacting with carbon monoxide and water in the presence of nickel carbonyl, giving acrylic acid:⁴⁹³



Reaction takes place rapidly at 40 to 42° and the yields are excellent. Hydrochloric acid is added to combine with the nickel freed in the course of the reaction.

Substituted acetylenes also undergo this reaction, forming α -substituted acrylic acids, α -phenylacrylic acid, $CH_2:C(C_6H_5)COOH$, resulting, for example, from phenylacetylene. Unsymmetrical disubstituted acetylenes, $RC \equiv CR'$, yield two isomeric products $RC(COOH) = CHR'$ and $RCH = CR'COOH$. Hexylacetylene gives *n*-7-octene-7-carboxylic acid, $CH_3(CH_2)_5C(=CH_2)COOH$; amyl methylacetylene yields β -amyl- α -methylacrylic acid as the principal product, and 1-butyne-3-ol gives 2-hydroxy-3-butene-3-carboxylic acid,



When alcohol is employed in the reaction in place of water, an ester of acrylic acid is formed:



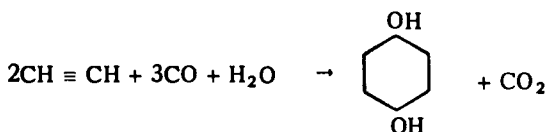
Similarly, thioacid esters, $CH_2 = CHCOSR$, are formed with mercaptans, amides



with amines $HNRR'$, and acid anhydrides $CH_2 = CHCOOCOR$ with carboxylic acids $RCOOH$.

Since acetylene reacts with nickel carbonyl in the presence of an inorganic acid forming acrylic acid, the catalyst is gradually destroyed. It can be regenerated by converting the nickel salt present in solution to hexamminonicklous chloride by the addition of somewhat more than the required quantity of ammonia, and treating the solution at 80° or at a higher temperature with carbon monoxide under 50 to 200 atm pressure. The nickel is converted quantitatively to nickel carbonyl which separates as a heavy oil.

The reaction of acetylene, or substituted acetylenes with *iron pentacarbonyl* in the presence of basic compounds and water results in the formation of hydroquinone or substituted hydroquinones. Thus, acetylene under pressure reacts rapidly at 60-75° in the presence of monoethanolamine to form hydroquinone:

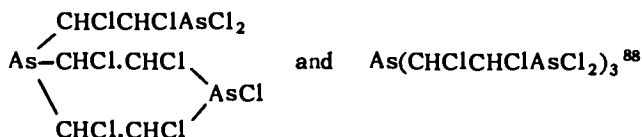


Reaction with Phosphorus and Arsenic Halides

Phosphorus pentachloride reacts with phenylacetylene in benzene solution, probably forming the compound $\text{C}_6\text{H}_5\text{CCl} = \text{CHPCl}_4$, which is transformed to $\text{C}_6\text{H}_5\text{CCl} = \text{CHPO}_3\text{H}_2$ on hydrolysis. Benzylacetylene, heptyne, etc. react in a similar manner. Negative results have been obtained with phenylethylacetylene, *p*-nitrophenylacetylene, tolane, and a number of other acetylenic compounds.³⁶¹

Phosphorus trichloride reacts with long chain acetylenic acids forming addition compounds.³⁶²

Arsenic trichloride reacts with acetylene to form tris-(β -chlorovinyl)arsine as the principal product, with smaller amounts of (β -chlorovinyl)dichloroarsine and bis-(β -chlorovinyl)-chloroarsine.⁸⁷ The use of a deficiency of acetylene results in the formation of the secondary and tertiary arsine, a large proportion of the trichloride remaining unchanged. The reaction apparently proceeds through the intermediate formation of the compound $\text{As}(\text{CHClCHCl})_3\text{As}$, further reaction with additional trichloride giving successively



Hydration of Acetylenic Compounds

The addition of the elements of water to the acetylenic triple bond results in the formation of a carbonyl compound in accordance with the following equation:

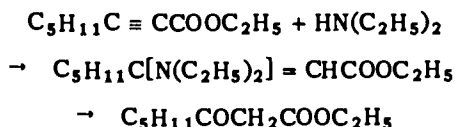


The reaction leads to the formation of acetaldehyde with acetylene; but with all other acetylenic compounds a ketone is obtained, the oxygen never becoming attached to a terminal carbon atom in monosubstituted acetylenes:



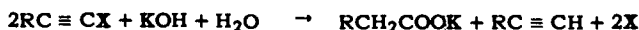
Reaction may be brought about with both mono- and disubstituted acetylenes by heating with water at 325°. ⁸⁹ A better method is to dissolve the hydrocarbon in concentrated sulfuric acid and subsequently to dilute with water, ⁹⁰ although long contact with a somewhat dilute acid induces polymerization of the hydrocarbon. ⁹¹ Hydration with concentrated sulfuric acid proceeds particularly well with those acetylenic compounds in which a phenyl, carbonyl, or carboxyl group is present in the vicinity of the triple bond. ⁹²

Alkyl acetylene carboxylic acids, $RC \equiv CCOOH$, are transformed to β -keto acids when heated with alcoholic potassium hydroxide. ⁹³ With amines, esters of such acetylenic acids yield amino acids which, when hydrolyzed with oxalic acid in ethereal or alcoholic solution, form β -keto acids:

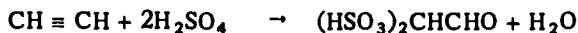


Acetylenic nitriles also undergo this reaction. Amides of alkyl acetylene carboxylic acids give the keto amide directly on warming with 95% alcohol in the presence of piperidine.

Haloacetylenes are converted partially to saturated acids on treatment with alcoholic caustic:



Fuming sulfuric acid containing 50% sulfur trioxide absorbs acetylene, forming acetaldehyde disulfonic acid: ⁹⁴



Some methionic acid is also formed in this reaction.

Sodium bisulfite adds to α,β -acetylenic esters. ⁹⁵ The monosulfoethylene-carboxylic ester results on heating the acetylenic ester with 1.5 molecular proportions of the bisulfite in aqueous solution at 100° for 8 hours in a sealed tube.

Catalytic Hydration

Acetylene is readily hydrated when it is led into a hot solution of mercuric sulfate in aqueous sulfuric acid. ⁹⁵ A 5% solution of mercuric sulfate in 10% aqueous sulfuric acid may be used for the purpose. Other mercuric salts also act as catalysts for this reaction. An addition compound of acetylene with the mercuric salt is apparently formed as an intermediate and is subsequently hydrolyzed to aldehyde. ⁹⁶ Hydration may be brought about also by use of mer-

curic acetate in solution in 60% acetic acid.⁹⁷ Mercury acetamide or mercury toluene-*p*-sulfonamide may also serve as catalysts;⁴⁹⁴ These reagents make possible the hydration of acid-sensitive compounds under substantially neutral conditions.

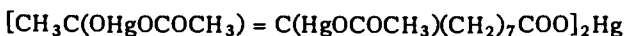
The mercuric sulfate catalyst is prepared by dissolving 1 part of mercuric oxide in 56 parts by weight of 45% sulfuric acid. The reaction is carried out at 15-20°. Hydration may be effected successfully at 60-80° by decreasing the concentration of the acid and passing a large excess of acetylene through the liquid.³⁶⁴ The reaction may be carried out at 68° under slight pressure, using 25% acid.³⁶⁵ The process is continuous, the unreacted acetylene carrying away the acetaldehyde as it is formed. Sulfuric acid of 25-35% strength is used. The catalyst consists of mercuric sulfate stabilized with ferric sulfate or acetate, or with manganese dioxide. The temperature is maintained between 60 and 80°.³⁶⁶

Two difficulties have been encountered in commercial practice: the aldehyde could not be removed readily from solution, and the mercury catalyst was inactivated rather rapidly, due either to reduction to metallic mercury, or conversion to insoluble organomercury compounds.⁹⁶ The aldehyde may be swept out of solution with an excess of acetylene.

Successful results are obtained, on the laboratory scale, by passing acetylene into a 3% mercuric sulfate solution in 96% acetic acid at 30°.

Salts of other metals such as zinc, cadmium, or magnesium have also been proposed as catalysts.

Homologs of acetylene and other acetylenic compounds are also hydrated to ketones by use of a mercury salt as a catalyst.⁹⁸ Disubstituted acetylenes give white precipitates with mercuric salts; these solids give ketones when treated with acids.²⁹ The structure of the mercury complexes obtained from 8-decyne-1-carboxylic acid was shown to be



and $[\text{CH}_3\text{C}(\text{HgOCOCH}_3) = \text{C}(\text{OHgOCOCH}_3)(\text{CH}_2)_7\text{COO}]_2\text{Hg}$. In general a solution of mercuric sulfate in sulfuric acid or mercuric acetate in acetic acid are employed as the reagent. The operation may be carried out in two steps, precipitation of the mercury complex and its subsequent hydrolysis.³⁶⁷ In the case of disubstituted acetylenes $\text{R}_1\text{C} \equiv \text{CR}_2$ the oxygen adds at the carbon atom farther removed from the more electronegative group. If the polar characteristics of R_1 and R_2 are widely different then one product will predominate, while if R_1 and R_2 are closely similar, mixtures of the two possible products $\text{R}_1\text{COCH}_2\text{R}_2$ and $\text{R}_1\text{CH}_2\text{COR}_2$ will be formed. An exception to the orientation rule is the formation of the diketone $\text{C}_6\text{H}_5\text{COCOCH}_3$ from benzoylacetylene, $\text{C}_6\text{H}_5\text{COC} \equiv \text{CH}$, in the mercury catalyzed hydration of the latter.⁵²⁷ In general mixtures of *cis* and *trans* isomers are formed, the latter often almost exclusively. In the hydration of unsymmetrical acetylenic bodies, $\text{RC} \equiv \text{CR}'$, the formation of $\text{RCOCH}_2\text{R}'$ is favored by increase in the chain length of R, by branching of R, or by introducing electron attracting groups such as COOH , NO_2 , Cl etc. into R' .

Dialkylethynealcohols have been hydrated by stirring them with four parts by weight of a solution obtained by dissolving 50 gm of mercuric oxide in a mixture of 200 gm

concentrated sulfuric acid and 1 lit water. The white precipitate which first appears becomes fluid and separates as an oil. The aqueous layer is drawn off, heated and the oil is added drop by drop, steam distilling the hydroxy ketone formed.

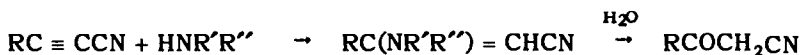
In certain cases it is of advantage to carry out the reaction in the presence of 50 to 75% of an organic solvent miscible with water. Thus, *dimethyldiacetylene* is best hydrated in an aqueous alcoholic solution by means of mercuric chloride.³⁶⁸ 1-Heptyne and 1-Octyne have been hydrated at 60 to 80° in aqueous acetone, acetic acid, or in 70% methanol.³⁶⁹ The two possible isomeric ketones are formed in nearly equivalent amount. If a keto group is present in the α -position to the triple bond, only the β -diketone is formed. With α -diynes also the β -diketone is the sole product.

Vinylacetylene has been hydrated to *methyl vinyl ketone* in the presence of mercury, calcium and silver salts. The reaction is usually carried out in aqueous acetic, sulfuric or phosphoric acid.³⁷⁰ Diacetylbutyl ether and 1-butane-3-one are byproducts of the reaction. In the carbinol $\text{CH}_3\text{CH}=\text{CHCH}(\text{OH})\text{C}\equiv\text{CH}$, the alcohol group is converted to a keto group and the final product of hydration is a diketone.³⁷¹ The hydration of acetylenic alcohols $\text{RC}\equiv\text{CCH}_2\text{OH}$ with mercuric acetate-acetic acid catalyst yields the α,β -unsaturated ketones $\text{RCOCH}=\text{CH}_2$, apparently as a result of the dehydration of the primary reaction product.²⁹⁵

Acetylenic acids have been effectively hydrated with 10% alcoholic potassium hydroxide.³⁷² This method is claimed to be superior to that utilizing mercury salts. It is not universally applicable, and *tert*-butylpropionic acid remains unchanged on refluxing with alcoholic potassium hydroxide for several hours.

Acetylenic esters have been hydrated by dissolving in concentrated sulfuric acid and pouring the solution on ice after standing for a short period.³⁷³ With *p*-nitrophenylpropionic acid, however, it is necessary to allow the solution of the ester in sulfuric acid to stand at 35 to 40° for 12 hours in order to complete hydration.³⁷⁴ The free *o*-nitrophenylpropionic acid gives ethyl isatogenate by the treatment.

The best method of hydration of α,β -acetylenic nitriles to the corresponding keto nitriles is to convert them to β -amino- α,β -ethylenic nitriles by the addition of ammonia or an amine and to hydrolyze the amino nitrile.³⁷⁵



Hydrolysis may be effected by use of an aqueous solution of oxalic acid, dilute hydrochloric acid or even with an aqueous solution of picric acid.

Acetylenic compounds may be hydrated by use of a mixture of mercuric oxide, the boron trifluoride-ether complex and trichloroacetic acid as a catalyst.⁵²⁸

Acetone has been made by the hydration of acetylene under pressure with steam in the presence of metallic oxides, hydroxides, carbonates, or acetates. The reaction may be carried out in the temperature range 250-450° and under three to ten atm pressure. Hydroxides, oxides, or carbonates of thorium, and double salts of the same metal such as potassium thorium carbonate, are effective catalysts.⁹⁹ Oxides, carbonates, or acetates of alkalineearth metals and of zinc, tin, aluminum, and magnesium, as well as of metals, the acetates of which yield acetone on heating, have been claimed as catalysts.¹⁰⁰

In commercial practice, a mixture of 78.8% zinc oxide and 21.2% ferric oxide is used.

It is deposited on steel balls 12 mm in diameter in the proportion of 1:15 and dried at 110°. The reactor tubes are 125 mm in diameter and 135 cm long. They are heated at 450° with a molten salt bath. The gases pass through these tubes at the rate of 450 lit per hour. The yields are stated to be in the neighborhood of 95% based on the acetylene consumed.

Reaction with Fused Alkalies

Acetylene reacts with fused alkalies to form acetates. The reaction is carried out by passing acetylene into a fused mixture of anhydrous sodium- and potassium hydroxides at 220°. The presence of a small amount of water materially improves the yield and purity of the product. The reaction proceeds slowly below 220°, while above 325° considerable decomposition of the acetate is observed. Utilization of acetylene is high, the loss amounting to 2-5%; the yield of acetate on the basis of caustic consumed is about 96%.

The reaction may be initiated with a mixture of fused hydroxide and acetate. Water may be introduced into the reaction zone in various ways, as steam, or by the addition of aqueous caustic. A very satisfactory method is to saturate the acetylene employed in the reaction with water vapor at 80°.

Reaction with Alcohols and Phenols

Alcohols combine with acetylene in the presence of catalysts to form vinyl ethers in accordance with the scheme:¹⁰¹



Alkaline substances, such as alkali and alkaline earth hydroxides and alcoholates, as well as compounds with a markedly alkaline reaction, such as potassium- or sodium cyanides, promote reaction. The most favorable temperature range is 150-160°.¹⁰²

The reaction may be carried out, for example, by passing acetylene under pressure into an alcoholic solution of an alkali metal hydroxide or alcoholate heated to 80-250°. Vinyl ethers have been prepared by this method from simple alcohols, carbohydrate derivatives, terpene alcohols, and hydroxy alkylamines.

Reaction with the lower alcohols such as methyl, ethyl, and propyl alcohol must be carried out under pressure. A continuous process is adopted in commercial practice in which compressed acetylene diluted with nitrogen, and the mixture of alcohol and catalyst are introduced into a tower. Alcohol containing potassium hydroxide is introduced at the base of the tower and the acetylene-nitrogen mixture containing 60% by volume acetylene is passed into the tower through distributors. The vinyl ether formed is drawn off in the vapor form and is freed from the accompanying alcohol vapors in a dephlagmator, condensed, and collected. The liquid ether is kept near its boiling point in the system in order to free it of dissolved acetylene. A portion of the waste gases is bled out, the acetylene carried away with it being recovered. Acetylene is introduced into the returning gases to bring its concentration to 60%. A portion of the tower base liquid is also drawn off continuously and worked up separately. The partial pressure of the acetylene in the entering gases is 10 atm.

Vinyl methyl ether may be prepared by this method from methanol and acetylene by reaction in the temperature range 160-200°, in the presence of 1 to 2% potassium hydroxide. The most favorable temperature range for the reaction with ethyl alcohol is 150-160° in the presence of 5% potassium hydroxide.

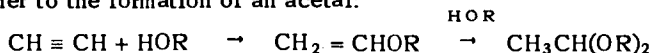
The reaction of acetylene with primary and secondary alcohols of the aliphatic series, up to nonyl alcohol, takes place very rapidly. The reaction velocity decreases with increase in the molecular weight of the alcohol, and is greater with primary alcohols than secondary alcohols. The reaction proceeds slowly with tertiary alcohols. A variety of products are obtained with di- and polyhydric alcohols due to varying degrees of vinylation and acetal formation. Reaction fails to proceed or proceeds slowly if the carbon atom bearing the hydroxyl group is in the vicinity of an unsaturated carbon atom, as in allyl and crotyl alcohols. The reaction proceeds well, however, if the double bond is in a remote position, as in oleyl alcohol. The reaction is applicable to hydroaromatic alcohols and phenols, but fails with compounds in which the hydroxyl group has a strongly acid character as in alizarin.

Reacting with vinyl acetylene in the presence of sodium alkoxide at 100°, alcohols yield 1-alkoxy-2-butyne, $\text{CH}_3\text{C}:\text{CCH}_2\text{OR}$.¹⁰³ Treatment of these with alcoholic potassium hydroxide at 150° results in the formation of 2-ethoxybutadiene, $\text{CH}_2 = \text{CHC}(\text{OC}_2\text{H}_5) = \text{CH}_2$, in poor yield.¹⁰⁴ The methanolic derivative possesses the allene structure, $\text{CH}_2 = \text{C} = \text{C}(\text{OCH}_3)\text{CH}_3$.

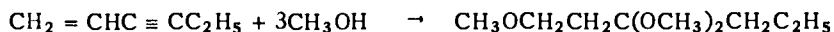
Mercuric salts in the presence of strong acids such as sulfuric or sulfonic acids are effective catalysts for the addition of alcohols to acetylenic bonds.¹⁰⁵ Alcohols with three or more carbon atoms give poor yields because of the dehydrating effect of sulfuric acid.

Solutions of mercuric oxide in methoxyfluoboric acid, CH_3OHBF_3 , or the complex, $(\text{C}_2\text{H}_5)_2\text{O} \cdot \text{BF}_3$, are excellent catalysts for the addition of dihydric alcohols to acetylene. They are, in fact, much superior to mercuric sulfate activated by sulfuric or other acids. These catalysts are effective in very low concentrations.¹⁰⁶ The addition of monohydric alcohols other than methanol is not effected by this catalyst, but addition to alkyl acetylenes can be effected by use of a catalyst prepared by warming a solution of the complex $(\text{C}_2\text{H}_5)_2\text{O} \cdot \text{BF}_3$ in methanol with mercuric oxide and adding a little trichloroacetic acid. Branched chain or *iso* alcohols fail to react, however, under the influence of this catalyst.¹⁰⁷

The reaction of acetylenic compounds with alcohols in the presence of acid catalysts, including mixtures of mercuric salts, and in the presence of mercuric chloride-boron fluoride catalyst¹⁰⁸ does not stop at the first stage, but proceeds further to the formation of an acetal:



Double bonds not conjugated with a triple bond are unaffected,⁵²⁹ but conjugated enynes react with three molecular equivalents of alcohol:

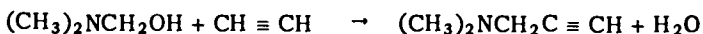


Catalysts with alkoxy fluoboric acids have the advantage over those with sulfuric acid in bringing about the formation of acetals in that they have a longer life, and are effective in low concentrations. Moreover, they have no oxidizing properties and show less tendency to cause cleavage of water or hydrogen halides from the reaction products. These catalysts have been used successfully for the preparation of cyclic acetals from

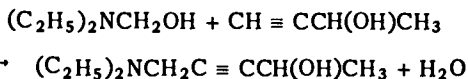
acetylene and glycols. The presence of small quantities of water causes the formation of tarry products in the preparation of ethylene glycol acetal by this method.¹⁰⁹

The reaction of acetylene with alcohols can also be carried out in the *vapor phase*, by passing a mixture of acetylene with the vapors of alcohol over a strongly basic substance, such as soda-lime, at 150-350°. The method has not assumed technical importance, however.

The reaction of acetylene with alkylolamines in the presence of copper acetylide results in the formation of propargylamines, reaction proceeding in some instances at an appreciable rate even at room temperature in the liquid phase,¹¹⁰ while in other cases it is necessary to heat to 40-60°. Dimethylmethanolamine reacting with acetylene at 25° gives dimethylpropargylamine in good yield,



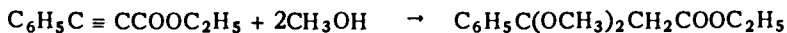
together with a little tetramethyldiaminebutyne. Similarly the reaction of 3-butyne-2-ol and dimethylolamine in acetic acid solution, in the presence of copper acetylide catalyst, leads to the formation of the corresponding acetylenic amino alcohol in theoretical yield:



Reduction of this amino alcohol gives 1-dimethylamino-4-pentanol, which is an intermediate in the preparation of Plasmochin. The corresponding amine, dimethylamino-4-pentylamine, together with the acetylenic amino alcohol form intermediates in the preparation of atebaine.

Acetylenic compounds, in general, behave toward alcohols in the same manner as acetylene. Compounds in which the triple bond is conjugated with a phenyl or carboxyl group add primary alcohols very readily in the presence of sodium alkoxides.¹¹¹ Thus, alcohols ROH readily add at the triple bond of phenylacetylene at 135° in the presence of potassium hydroxide or sodium ethoxide to form β -alkoxystyrenes, $\text{C}_6\text{H}_5\text{CH} = \text{CHOR}$, in yields ranging from 68 to 77%.¹¹² Addition takes place with propargyl acetal and acetylenic glycols.¹¹³ A 1,4-addition takes place with vinylacetylene initially but the products rearrange to 1-alkoxy-2-butyne.¹¹⁴ Treatment of alkynes with alcoholic caustic results principally in the rearrangement of the compound.¹¹⁵

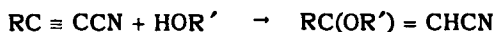
Acetylenecarboxylic esters react with two molecules of alcohol in the presence of sodium alcoholate to form ketals of β -keto esters:¹¹⁶



Increased yields have been obtained in some instances by use of a boron trifluoride-mercuric oxide catalyst. Attempts to cause secondary alcohols to react with acetylenic hydroxy esters in the presence of sodium alkoxides have been unsuccessful.

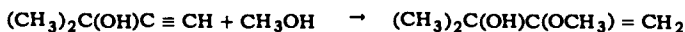
The addition of alcohols to α,β -acetylenic nitriles has been effected by refluxing the nitrile with a solution of potassium hydroxide in the alcohol.³⁷⁶

The reaction results in the formation of β -alkoxy- α,β -ethylenic nitriles:



A mixture of the alkoxyethylenic nitrile and the β,β' -dialkoxy derivative of the saturated nitrile, $RC(OR')_2CH_2CH$, were obtained when the reaction was carried out in the presence of sodium alkoxide.

The reaction of dimethyl ethynyl carbinol with methanol under the action of mercuric oxide-boron trifluoride catalyst results in the formation of the simple as well as a complex internal ketal:¹¹⁷

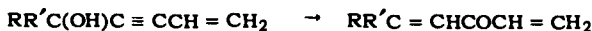


The reaction with higher aliphatic alcohols also results in the formation of similar compounds,¹¹⁸ although *n*-amyl alcohol only gives the simple acetal. A dioxalan,

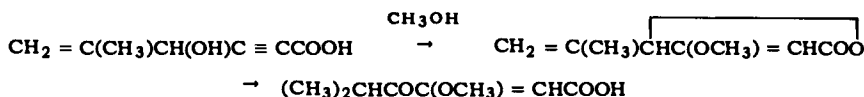
$\overbrace{OCH_2CH_2OC(CH_3)C(OH)(CH_3)_2}$, is obtained with ethylene glycol.¹¹⁹ Many other acetylenic carbinols behave in a similar manner. Propargyl carbinol does not undergo bimolecular condensation and gives only a vinyl ether, $CH_2 = C(OCH_3)CH_2CH_2OH$ and a ketone acetal, $CH_3C(OCH_3)_2CH_2CH_2OH$.

An intractable mixture was obtained from the reaction of methyl alcohol with the

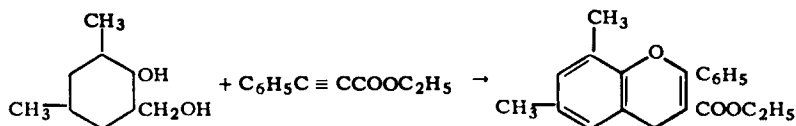
acetylenic carbinol, $\overbrace{CH_2(CH_2)_4C(OH)C \equiv CH}$, under the influence of mercuric oxide-boron trifluoride catalyst. Vinylacetylenic carbinols, $RR'C(OH)C \equiv CCH = CH_2$, isomerized to a doubly unsaturated ketone, the latter were converted to the ether of an unsaturated keto alcohol through the addition of a molecule of alcohol:¹²⁰

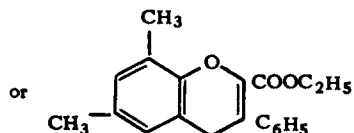


Dihydropenicillic acid has been obtained by the hydrolysis of the lactone resulting from the reaction of methanol and 4-methyl-4-pentene-1-yne-3-ol-1-carboxylic ester.³⁷⁷



A benzopyran derivative results through the reaction of phenylpropionic ester with 2-hydroxy-3,5-dimethylbenzyl alcohol at 200° in the absence of a catalyst:³⁷⁸





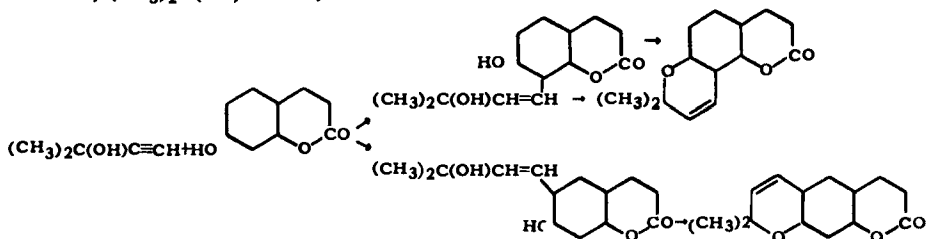
Phenols react with acetylene under the action of alkalis. Sodium phenolate, or preferably potassium phenolate serve as catalysts:



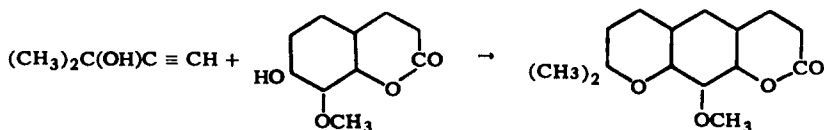
Reaction in the presence of zinc or cadmium salts results in the formation of vinyl phenols, the vinyl group entering the benzene nucleus.¹²¹

The vinyl phenols formed polymerize spontaneously to high molecular compounds of the type of "Koresines." The latter are condensation products resulting from the reaction of *p*-tert-butylphenol with acetylene in the presence of zinc naphthenate. It is possible that a hydroxy styrene is first formed and polymerizes to a chain compound, $-\text{CH}_2[\text{C}_6\text{H}_3(\text{OH})\text{R}]\text{CH}_2\text{CH}_2[\text{C}_6\text{H}_3(\text{OH})\text{R}]\text{CH}_2-$.

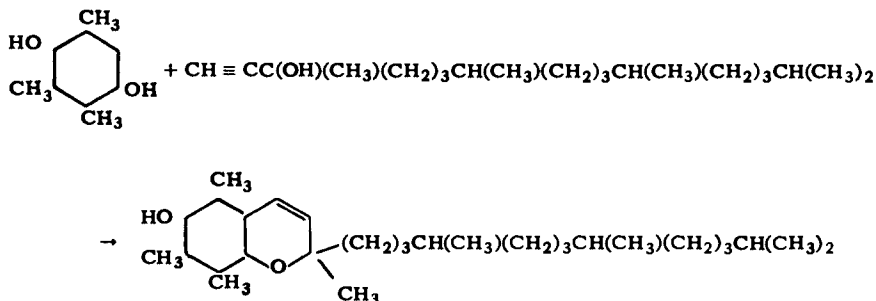
The addition products of phenols with acetylenic carbinols cyclize to heterocyclic rings. *Sesatin* and *xanthyletin* have been obtained through the condensation of the carbinol, $(\text{CH}_3)_2\text{C}(\text{OH})\text{C} \equiv \text{CH}$, with unbelliferon:¹²²



Luvagetin has been obtained similarly through the condensation of the same carbinol with the 8-methyl ether of daphnetin:¹²³

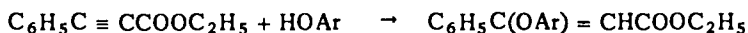


Vitamin E analogs have been synthesized similarly:¹²⁴

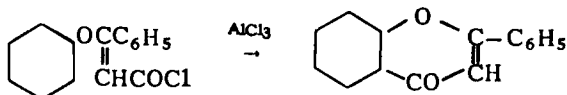


The condensation was carried out in the presence of zinc chloride at 170°.

Phenolic compounds have been condensed with phenylpropionic ester to β -phenoxycinnamic esters:³⁷⁹



Chlorides of the corresponding acids have been cyclized to flavones:³⁸⁰



Phloroglucinol reacting with propionic acid in the presence of zinc chloride and acetic acid gives 5,7-dihydroxy-4-phenylcoumarin in 80% yield:³⁸¹

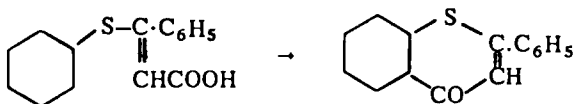


Addition of phenols to α,β -acetylenic nitriles is brought about in the same manner as that of alcohols.³⁸² In the presence of a molecular equivalent of potassium hydroxide, only the β -aryloxy- α,β -ethylenic nitriles are formed.

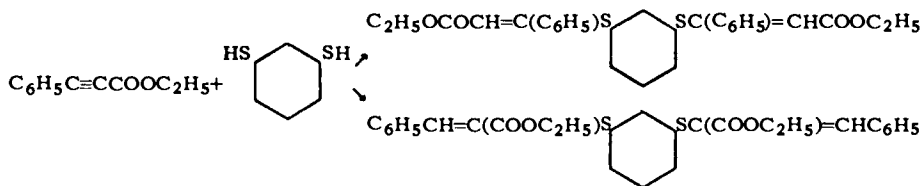
Thiophenols add to acetylenic acids in the same manner as phenols. Addition takes place in the presence of sodium derivatives of thiophenols:³⁸³



The adducts have been cyclized to thioflavones by treatment of the free acids with phosphorus pentachloride followed by heating with aluminum chloride:³⁸⁴



The reaction of dithioresorcinol with phenylpropionic acid results in the formation of a normal as well as an abnormal adduct:³⁸⁵

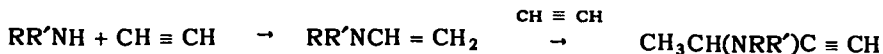


Addition of vinylacetylene to phenolic compounds takes place at the ethylenic bond of vinylacetylene, the triple bond remaining intact.

Reaction of Acetylenic Compounds with Amines and Related Compounds

Secondary amines react with acetylene under pressure at 180° in an inert solvent, such as hexahydroxylene, to form vinylamines, $\text{RR}'\text{NCH} = \text{CH}_2$. Pyrole,

indole, carbazole, and imidazoles undergo this reaction. In the presence of heavy metal acetylides, secondary amines react with two molecular equivalents of acetylene to form 3-amino-1-butyne, vinylamines being an intermediate product of the reaction:¹²⁵



The temperature at which the reaction proceeds varies with the nature of the amine. Aniline reacts at room temperature, but many other amines react only at 100°. The reaction involves risks of explosion, and antioxidants such as β, β' -dinaphthol are used.

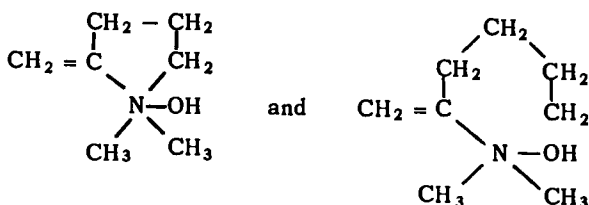
The reaction has been carried out successfully with primary and secondary aliphatic, cycloaliphatic, and heterocyclic amines. Primary and secondary aromatic amines undergo the reaction when they are present partly in the form of their organic salts.¹²⁶ The resulting acetylenic amines may be transformed to amino ketones by hydrolysis in the presence of mercury salts.¹²⁷ They may be transformed to conjugated aminodienes, $\text{CH}_2 = \text{C}(\text{NRR}')\text{CH} = \text{CH}_2$, by contact with oxides of aluminum or iron at 250°. ¹²⁸ Such 2-amino butadienes are also formed through the reaction of secondary amines with vinylacetylene in toluene solution in the presence of cuprous chloride under pressure at 105°. ¹²⁹

The polymeric form of N-vinylpyrrolidone has been used as a blood plasma substitute under the name "Peristone." The polymer of N-vinylcarbazole (Luvican, Polectron) is highly heat resistant and possesses valuable electric properties.

Tertiary amines may be vinylated with acetylene in the absence of a catalyst. *Neurin* may be obtained, for example, by the addition of a molecule of acetylene and of water to one of trimethylamine:⁴⁹⁶



An internal condensation of this type has been observed with 5-dimethylamino-pent-1-yne and 6-dimethylaminohex-1-yne giving cyclic quaternary hydroxides⁵³⁰



The reaction of primary amines with acetylene proceeds in a complicated manner. Aniline yields a quanildine and a tetrahydroquinaldine.¹³⁰

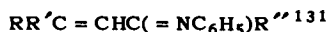
Vinylamine is formed as an intermediate in the reaction of ammonia with acetylene in the presence of copper phosphate; the end product of the reaction is 2-methyl-5 ethylpyridine.

The addition of amines to acetylenic compounds is greatly facilitated if the triple bond is conjugated with an electron attracting group. Addition at the triple bond occurs preferentially if a similarly activated doubled bond is present in the molecule.⁵³¹ The vinylamines formed may be readily hydrolyzed to the corresponding ketones by treatment with acids.

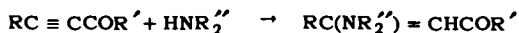
The condensation of amines with acetylene may be effected in the vapor phase in the presence of zinc halides.³⁸⁶ The reaction with primary amines proceeds in a complicated manner. The reaction with diarylamines, pyridine, carbazole, etc., has been carried out successfully under 25 to 50 atm pressure in the presence of a diluent gas.

Dichloroacetylene reacts with great ease with amines and ammonia. With diethylamine, the unstable dichloroamine $\text{ClCH} = \text{CClN}(\text{C}_2\text{H}_5)_2$ is formed which hydrolyzes to N-diethyl chloroacetamide, $\text{ClCH}_2\text{CON}(\text{C}_2\text{H}_5)_2$. With an excess of diethylamine, the compound $\text{ClCH} = \text{C}[\text{N}(\text{C}_2\text{H}_5)_2]_2$ is obtained.

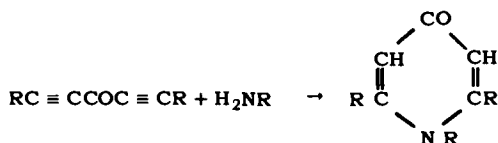
Acetylenic chlorides of the type $\text{RR}'\text{CClC} \equiv \text{CR}'$, in which R's are all aromatic groups react with aniline to form the compounds $\text{RR}'\text{C}(\text{NHC}_6\text{H}_5)\text{C} \equiv \text{CR}'$, and



Amino vinyl ketones result from the reaction of secondary amines with acetylenic ketones

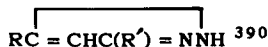


Resinous products are obtained with primary amines. With ketones containing both an olefinic and acetylenic bond, addition takes place at the triple bond.³⁸⁷ Diacetylenic ketones, $\text{RC} \equiv \text{CCOC} \equiv \text{CR}$ combine with one molecular equivalent of the amine. With a primary amine a γ -pyrone is formed quantitatively providing R is an aliphatic residue:³⁸⁸



Amines add readily to α, β -acetylenic esters forming β -amino- α, β -ethylenic esters.³⁸⁹ With primary aromatic amines and acetylenedicarboxylic ester, the saturated imines $\text{ROCOC}(=\text{NAr})\text{CH}_2\text{COOR}$ are formed.

Hydrazine reacts with acetylenic ketones, $\text{RC} \equiv \text{CCOR}'$, to form pyrazoles



The acetylenic aldehyde $\text{CH} \equiv \text{CCHO}$ reacts with phenylhydrazine to form phenylpyrazole, $\text{C}_6\text{H}_5\text{NCH} = \text{CHCH} = \text{N}$.

Acetylene and monosubstituted acetylenes undergo a Mannich type reaction with dialkyl amines and formaldehyde:

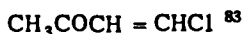


Aryl acetylenes and vinyl acetylene react readily, while acetylene reacts only in the presence of copper acetylide catalyst.¹³² Amino acetylenes thus derived from phenylacetylene have been hydrated to aminopropiophenones



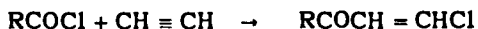
Reaction of Acetylenic Compounds with Acyl Chlorides; Other Addition Reactions

Acetyl chloride reacts readily at 15° with acetylene in the presence of aluminum chloride forming the somewhat unstable β -chlorovinylketone,



Mono- and disubstituted acetylenes also react with acetyl chloride in the presence of stannic chloride, zinc halides, boron trifluoride, etc., although the yields of chlorinated ketones are low.⁸⁴

Acetylene reacts with other acid chlorides in the presence of aluminum chloride to form β -chlorovinyl ketones:¹³³



Isobutyl β -chlorovinyl ketone is obtained in 55% yield by adding 8 parts aluminum chloride to a solution of 10 parts isovaleryl chloride in 20 parts petroleum ether cooled to 0 to 5°, and conducting acetylene through the mixture for two hours. The chlorovinyl ketone is isolated by adding ice water to the mixture, extracting with benzene, washing the extract with aqueous potassium carbonate, drying, and finally evaporating off the benzene.

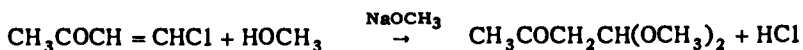
Chlorinated olefins are formed in some cases; they are the principal compounds formed with disubstituted acetylenes.³⁹¹ With oxalyl chloride, addition of chlorine and the COCl group takes place with liberation of carbon monoxide:³⁹²



β -Chlorovinyl ketones reacting with Grignard reagents give the halomagnesium derivatives of unsaturated halo alcohols which may be converted to unsaturated ketones by anionotropic rearrangement:



β -Keto acetals or β -keto ketals are obtained by the action of methanolic sodium methoxide on the chlorovinyl ketones:



Dimethyl carbonate reacting with acetylene in liquid ammonia in the presence of sodamide gives methyl methoxyacrylate, $\text{CH}_3\text{OCH} = \text{CHCOOCH}_3$, together with other products.⁸⁵ Double bonds conjugated with the triple bond remain unaffected in this reaction.

Monosubstituted acetylenes react with *sulfur dioxide* at ordinary temperature in the presence of paraldehyde containing peroxides or better, ascaridole, in the same manner as certain olefinic compounds, forming polymeric sulfones.⁸⁶ Mixtures of olefins and monosubstituted acetylenes yield mixed polymeric sulfones. Disubstituted acetylenes and acetylenic compounds of the type $\text{R}_1\text{R}_2\text{CHC} \equiv \text{CH}$ fail to react.

Chloro ethers reacting with vinylacetylene in the presence of bismuth chloride

Reduction of Acetylenic Compounds

Acetylene may be hydrogenated by use of reducing agents, or with hydrogen in the presence of catalysts.¹³⁸ Partial reduction to ethylene or complete reduction to ethane may be accomplished by the proper choice of the catalyst and the conditions under which the reduction is carried out. (*)

Platinum black causes complete reduction even at room temperature when an excess of hydrogen is used.¹³⁹ Hydrogenation in the presence of platinum sponge at 180° results in the formation of ethane, together with considerable quantities of liquid hydrocarbons. Hydrogenation of acetylene to liquid products may be effected at higher temperatures under pressure.¹⁴⁰

Semi-hydrogenation of acetylene to ethylene may be achieved by use of *palladium hydrosol* as a catalyst. Palladium is also suitable for the partial hydrogenation of derivatives of acetylene, such as acetylenic carbinols. The labile derivatives are always formed when hydrogenation is effected rapidly, and the steric structure of the bodies concerned is not affected.³⁹⁷ The use of palladium catalyst is recommended when it is desired to stop the reduction at the ethylenic derivative.³⁹⁸

A palladium-calcium carbonate catalyst partially inactivated by treatment with lead acetate is specific for the partial hydrogenation of the triple bond. The specificity is further enhanced by the addition of quinoline.⁵³² Hydrogenation in the presence of such a catalyst comes to a standstill after the absorption of one mole hydrogen, and the formation of 86% of hydrogenated product. The catalyst has proven of great value in the synthesis of carotenoids. A selective Raney nickel catalyst produced by deactivation with zinc acetate has been described.⁵³³ Selective reduction of the acetylenic bond to an ethylenic bond by these catalysts is best carried out in light petroleum.

Selective reduction of the triple bond in acetylenic compounds containing ethylenic bonds may be accomplished providing the multiple bonds are not conjugated.⁵³⁴ If two triple bonds are present in the molecule, they may be both reduced to ethylenic bonds. Removal of the amino group from *tert*-amino acetylenes in the process of hydrogenation has been noted in several cases.

The ethylenic product obtained in the partial catalytic reduction of acetylenic bodies consists largely of the *cis*-isomer. One example of the nearly exclusive formation of the *trans*-isomer has been reported however.⁵³⁵ The partial catalytic reduction of acetylenic acetals results in the formation of the *cis*-ethylenic acetals; these, on hydrolysis, give the *trans* α,β -ethylenic aldehydes. Only a double bond adjacent to the acetal grouping is subject to this transformation. The method has been employed for the synthesis of the violet leaf perfume nona-2(*trans*)-6(*cis*)-dien-1-al.⁵³⁶

Partial hydrogenation of acetylene has been accomplished by passing a gaseous mixture consisting of 47% by volume of acetylene and 51% hydrogen over

(*) Acetylene is not attacked by atomic hydrogen.⁵⁷³

freshly reduced nickel from which all hydrogen has been previously removed,¹⁴² ethylene being then obtained in 80% yield. Nickel catalysts have been used extensively for the hydrogenation of acetylene in the gas or liquid phase.¹⁴³ A *nickel-molybdenum* catalyst gives ethylene almost exclusively at 55°, with a mixture of acetylene with a large excess of hydrogen; but at 70°, equal parts of ethylene and ethane are formed.¹⁴¹

Reduced copper deposited on silica gel is less active than nickel and requires higher temperatures, reduction taking place between 130° and 200°.¹⁴⁴ Cobalt, copper chromite, iron, aluminum and cerium oxide, and tellurium also possess catalytic activity.¹⁴⁵ A copper-zinc couple has been employed for the reduction of acetylenic hydrocarbons.³⁹⁹ Vinylacetylene has been converted to butadiene in almost quantitative yield by use of this catalyst.⁴⁰⁰ An active form of iron prepared by the method of Raney caused hydrogenation to proceed only to the ethylenic stage, when the reduction was carried out at 100° under 50 atm pressure. Nitrile groups, if present in the acetylenic compound, are not reduced under these conditions.⁴⁰¹ Chromous chloride is also specific in its action, and allows the reduction to be carried out to the desired stage.⁴⁰²

Steam inhibits the formation of oily polymerization products which otherwise appear when nickel and other metals are employed in the catalytic reduction of acetylene.¹⁴⁶

The triple bond in vinylacetylenes is reduced in preference to the ethylenic linkage.

The semi-reduction of acetylenic carbinols of the type $RR'C(OH)C \equiv CH$ or $RR'C(OH)C \equiv C(OH)RR'$ may be accomplished readily by use of palladium catalyst, because the second stage of the reduction takes place more slowly than the first,¹⁴⁷ while with acetylenic hydrocarbons the contrary is generally true.¹⁴⁸ Reduction takes place very slowly in isobutyl or isoamyl alcohol, and in acetone.¹⁴⁹

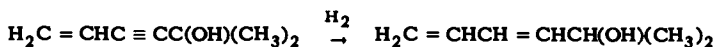
A colloidal palladium suspension in water containing starch in solution has been used effectively for the partial reduction of acetylenic glycols.¹⁵⁰ Reduction proceeds further when other catalysts are employed; partial reduction of acetylenic glycols can be achieved, however, by suspending the reduction after the calculated quantity of hydrogen has been absorbed.¹⁵¹

Platinum is eminently suited for the complete reduction of acetylenic carbinols to saturated carbinols, although reduction of the hydroxyl group also takes place on prolonged hydrogenation.¹⁵² Conversion to the saturated alcohol may be accomplished by suspending the reduction after the theoretical quantity of hydrogen has been absorbed.¹⁵³

Acetylenic glycols are converted to saturated dihydric alcohols by reduction in the presence of Raney nickel at moderately elevated temperatures.¹⁵⁴ Nickel catalysts have also been employed, however, for the semi-hydrogenation of acetylenic carbinols of the sex hormone series.¹⁵⁵

Copper, cobalt, and silver catalysts also bring about the complete hydrogenation of acetylenic glycols.

The triple bond in vinylacetylenic carbinols is attacked in preference to the double bond, partial hydrogenation in the presence of palladium catalyst yielding 1,3-butadienyl carbinols;¹⁵⁶



Acetylenic alcohols in which the hydroxyl group is attached to a carbon atom adjacent to a triply bound carbon are readily reduced by lithium aluminum hydride to *trans* ethylenes.⁵³⁷

Conjugated diacetylenes in which the conjugated system of triply bound carbon atoms is flanked on each side by carbinol groups are reduced to *trans-trans*-dienes with lithium aluminum hydride.⁴⁰³ Reduction of the acetylenic glycols $\text{RCH}(\text{OH})\text{C} \equiv \text{CCH}(\text{OH})\text{R}$ with lithium aluminum hydride leads to the formation of the dienes $\text{RCH} = \text{CHCH} = \text{CHR}$. The method has been employed for the preparation of cosinine,



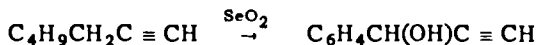
The reduction of acetylenic compounds has been carried out by use of *sodium* and *alcohol*.⁴⁰⁴ This method has the disadvantage that it may bring about isomerization of the product.⁴⁰⁵ A solution of an *alkali metal* in *liquid ammonia* is highly specific for the reduction of isolated triple bonds to ethylenic bonds, without the formation of detectable amounts of a saturated compound. The method is stereospecific and yields the *trans* ethylenic body.⁵³⁸ The reduction of mono-substituted acetylenes may be carried out effectively by this method in the presence of ammonium sulfate. Reduction of α -hydroxyacetylenes may be effected without fission of the propargylic hydroxyl group when the sodium derivative of the alcohol is employed. Phenyl ethers are dealkylated and halogen atoms are removed. Two triple bonds in the same molecule may be reduced. A non-terminal triple bond may be reduced with sodium and liquid ammonia without affecting a terminal triple bond in the same molecule by replacing the hydrogen of the terminal acetylenic groups with sodium by treatment with sodamide.

The reduction of acetylenic compounds has been effected electrolytically.⁴⁰⁶

Oxidation of Acetylenic Compounds

Acetylene is almost instantly oxidized by potassium permanganate.¹⁵⁷ Oxidation in acid solution results in the formation of carbon dioxide and formic acid, whereas in alkaline solution oxalic acid is formed.¹⁵⁸ α -Diketones are obtained when the oxidation is effected with dilute permanganate solution buffered with magnesium sulfate.⁵³⁹ On treatment of acetylene with dilute nitric acid in the presence of mercuric salts, oxalic acid is obtained in very good yield.¹⁵⁹

Acetylenic compounds may be converted to α -diketones by the action of selenium dioxide, providing carbon atoms adjacent to the triply bound carbons do not bear hydrogen atoms.⁵⁴⁰ Should hydrogen atoms be attached to the carbon atoms adjacent to the triply bound carbons, the result of oxidation with selenium dioxide is the formation of an α -hydroxyacetylene:⁵⁴¹



In either case the yields do not exceed 25%.

Ozone reacts with acetylene vigorously, and often with explosive violence.¹⁶⁰ The two gases react smoothly if sufficiently diluted with an inert gas. A mixture consisting of 1-2% ozone, 3-4% acetylene gives glyoxal in 94-96% yield.¹⁶¹ This dialdehyde may be recovered in the form of a concentrated aqueous solution by injecting water vapor or spray into the reaction mixture. The reaction of ozone with acetylene also proceeds smoothly in an indifferent solvent such as

methyl chloride, glyoxal and formic acid being the products obtained.¹⁶² The reaction of ozone with acetylenic bodies proceeds less vigorously than the reaction with the corresponding ethylenic compounds.⁵⁴² Conditions may be so adjusted as to give α -diketones in fair yields.⁵⁴³

Heated in a sealed tube to 300°, oxygen reacts rapidly with acetylene; reaction proceeds with explosive violence at 350° and at an appreciable rate even at 250°.¹⁶³

Derivatives of acetylene are generally oxidized to diketones or to carboxylic acids. The latter are formed through cleavage of the molecule of the acetylenic compound at the triple bond, occasionally with loss of a molecule of carbon dioxide and the resulting shortening of the carbon chain by one carbon atom.¹⁶⁴ Potassium permanganate, chromic acid, nitric and peracetic acids, and ozone have been used as oxidizing agents. Acetylenic carbinols are formed on treatment of alkyl acetylenes with selenium dioxide, through the oxidation of the methylene group adjacent to the triply bound carbon.¹⁶⁵ Diamylacetylene and similar hydrocarbons are converted to acetylenic ketones.¹⁶⁶

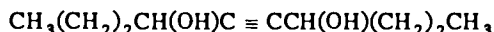
Unstable *peroxides* are formed when acetylenic hydrocarbons are allowed to remain in prolonged contact with air or oxygen.¹⁶⁷

The readiness with which acetylenic alcohols of the type $RCH(OH)C \equiv CH$ are oxidized depends on the character of the group R. Oxidation proceeds with decreasing ease in the order C_6H_5 , $CH_3CH = CH$, $CH_3CH_2CH_2$, CH_3 .

Secondary acetylenic alcohols of the type $RCH(OH)C \equiv CCH(OH)R$ are oxidized to acetylenic ketones $RCOC \equiv CH$ by chromic acid.¹⁶⁸

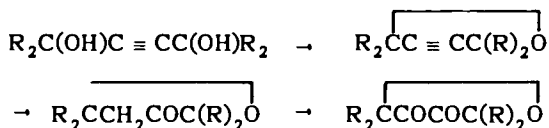
The solution of chromic oxide in sulfuric acid is added to the solution of the acetylenic compound in a ketone. The concentrations are so chosen that a two layer system is formed as the oxidation proceeds, and the ketone is thus eliminated from the zone of the reaction as rapidly as it is formed.⁴⁰⁷

Aromatic acetylenic glycols, $RCH(OH)C \equiv CCH(OH)R$, are converted by the same oxidizing agent to diketones, $RCOC \equiv CCOR$.¹⁶⁹ Diketones are also formed when R is the group $CH_3CH = CH-$,¹⁷⁰ but the compound



is oxidized to the keto-alcohol stage, further oxidation proceeding with difficulty.

Ditertiary glycols of the type $RR'C(OH)C \equiv CC(OH)RR'$, treated with chromic acid, are first transformed to cyclic compounds, and are subsequently oxidized to furan diones:¹⁷¹



Ozonolysis of the triple bond in acetylenic compounds results in the formation

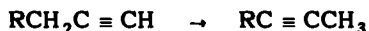
of carboxylic acids, generally in low yield.¹⁷² Glyoxal has been obtained in good yield by the reaction of dilute ozone with acetylene.¹⁷³

Oxidation of the triple bond in acetylenic compounds by permanganate does not follow the course observed with olefinic bonds.¹⁷⁴ It appears probable that oxygen or the elements of water first add at the triple bond, and subsequently hydrolytic cleavage takes place with the formation of acids. Oxidation with peracetic acid proceeds in a more complicated manner than with olefins.¹⁷⁵

Selenium dioxide, SeO_2 , oxidizes a methylene group in the proximity of a triple bond without affecting the latter. The resulting compound is an acetylenic alcohol.⁴⁰⁸

Isomerization of Acetylenic Compounds

Acetylenic compounds may undergo isomerization when heated, or when subjected to the action of acids or other agents. Thus, monosubstituted acetylenes having a vinyl group or a vinyl homolog as a substituent, isomerize when heated with alcoholic caustic to form disubstituted acetylenes:³⁰

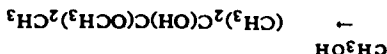
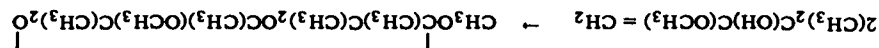


In general the treatment causes a shift of the triple bond toward the center of the chain. Compounds of the type $\text{R}_2\text{CHC} \equiv \text{CH}$ are converted to allenes,



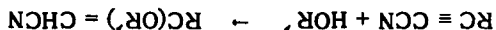
Many other acetylenic carbinols behave in a similar manner. Propargyl carbinol does not undergo bimolecular condensation and gives only a vinyl ether, $\text{CH}_2 = \text{C}(\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH})$.¹¹⁹

The reaction with higher aliphatic alcohols also results in the formation of allene compounds,¹¹⁸ although n-amyl alcohol only gives the simple acetal. A dioxolan,



The reaction of dimethyl ethynyl carbinol with methanol under the action of mercuric oxide-boron trifluoride catalyst results in the formation of the simple as well as a complex internal ketal.¹¹⁷

A mixture of the alkoxylethylenic nitrile and the β, β' -dialkoxylethylenic nitrile, $\text{RC}(\text{OR}')_2\text{CH}_2\text{CH}_2\text{CN}$, were obtained when the reaction was carried out in the presence of sodium alkoxide.



The reaction results in the formation of β -alkoxy- α, β -ethylenic nitriles:

The triple bond in acetylenic acids, $RC \equiv C(CH_2)_nCOOH$, may be made to migrate by adding hydrogen iodide to the triple bond and subsequently removing it by a convenient method.⁴⁰⁹

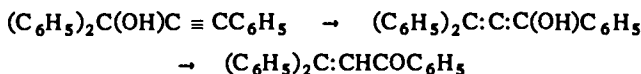
Diarylacetylenic compounds of the type $RCH_2C \equiv CR'$ are converted to allenes $RCH = C = CHR'$ by absorption on activated alumina at room temperature.⁵⁴⁴ Related rearrangements are observed in the dehalogenation of secondary α -chloroacetylenes $RCHClC \equiv CH$ to the allenes $RCH = C = CH_2$,⁵⁴⁵ and in the formation of allenecarboxylic acids $RR'C = C = C(R'')COOH$ through the reaction of carbon dioxide with Grignard compounds derived from α -bromoacetylenes



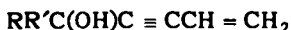
The latter transformation takes place also by the action of nickel carbonyl on the bromo compound.

Isomerizations Involving Migrations of Hydroxyl Groups; The Meyer-Schuster Rearrangement

A large number of molecular rearrangements observed with acetylenic compounds involve the migration of the hydroxyl groups or other negative groups or atoms within the molecule. The Meyer-Schuster rearrangement is typical of these transformations; it involves the migration of a hydroxyl group in an acetylenic compound, a subsequent adjustment resulting in the formation of an ethylenic ketone:¹⁸⁰



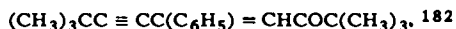
This is an anionotropic rearrangement induced by acids as well as thionyl chloride and acetic anhydride. The reagents commonly used are alcoholic sulfuric or hydrochloric acid. The vinylacetylenic carbinol, $CH_2 = CHC \equiv CC(OH)(CH_3)_2$, undergoes the transformation in acetone containing sulfuric acid, giving vinyl isobutyl ketone.¹⁸¹ Other vinylacetylenic alcohols of the type



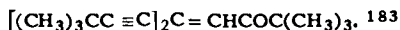
also undergo the transformation.

The transformation has been observed, to take place almost exclusively with compounds bearing at least one aromatic group, in one example, namely that of the compound $(CH_3)_2C(OH)C \equiv C(CH_2)_4CH_3$, the Meyer-Schuster rearrangement has been found to occur with an acetylenic carbinol containing only saturated aliphatic substituents.

Phenyl di(*tert*-butylethynyl) carbinol, $(CH_3)_3CC \equiv CC(OH)(C_6H_5)C \equiv CC(CH_3)_3$, undergoes the Meyer-Schuster rearrangement under the action of a mixture of concentrated sulfuric acid and acetic acid giving the α,β -unsaturated ketone



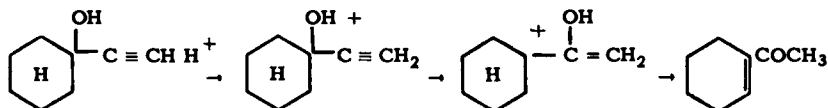
Tri(*tert*-butylethynyl)carbinol, $[(CH_3)_3CC \equiv C]_3COH$, is similarly converted to



The acetylenic glycol, $\text{HOCH}_2\text{C} \equiv \text{CCH}_2\text{OH}$, is isomerized to the unsaturated ketol, $\text{HOCH}_2\text{COCH}=\text{CH}_2$, on treatment with a 5% solution of mercuric chloride in 10% aqueous sulfuric acid. The transformation takes place at ordinary or slightly elevated temperatures, and is complete within 6 to 8 hours.

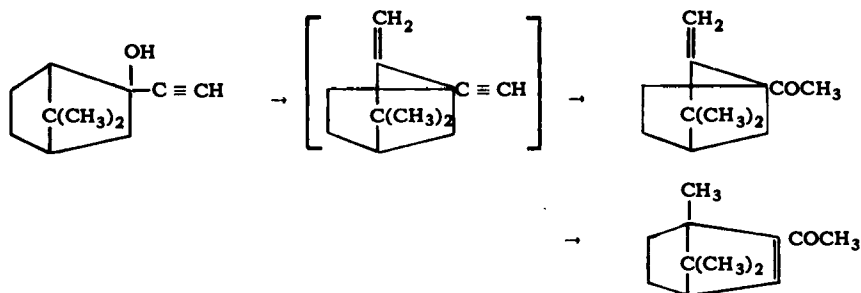
The isomerization of vinylacetylenic carbinols involves serious difficulties and requires milder conditions.¹⁸⁴ The rearrangement has been brought about by stirring the acetone solution of the carbinol with 2% mercuric sulfate for 4 hours, although the ketones are obtained in *small yield*.

The main product of the acid catalyzed rearrangement of tertiary ethynylcarbinol, $\text{RR}'\text{C}(\text{OH})\text{C} \equiv \text{CH}$, is an α,β -ethylenic ketone.⁵⁴⁷ This transformation, which is known as the *Rupe rearrangement*, takes place with 1-ethynylcyclohexanol:

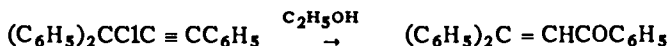


The acetylenic hydroxyester $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{C} \equiv \text{CCOOCH}_3$ rearranges to $\text{C}_6\text{H}_5\text{COCH}=\text{CHCOOCH}_3$ in the presence of triethylamine.⁵⁴⁸

The isomerization of ethynylbornyl alcohol has been achieved by treatment with formic acid, and results in the formation of 2-acetyl-6-hydroxycamphene, the conversion involving a Wagner transformation in addition to the Meyer-Schuster rearrangement:¹⁸⁵

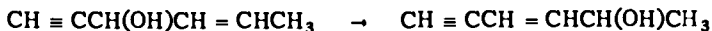


The Meyer-Schuster rearrangement of carbinols derived from acetylenic halides has been accomplished directly from the halides by boiling the compound with ethyl alcohol:¹⁸⁶



A similar transformation is effected by treating acetylenic ethers with cold 10% alcoholic sulfuric acid and, in certain cases, with hydrobromic acid.¹⁸⁷

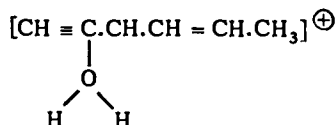
The migration of the hydroxyl group in acetylenic compounds containing an ethylenic linkage may take place over the latter, as with propenylethynylcarbinol, which undergoes an anionotropic rearrangement under the action of acids under mild conditions, to form an acetylenic vinylcarbinol:¹⁸⁸



The reaction is general for hydroxyacetylenes which contain a double bond system separated from a triple bond by a carbon atom bearing a hydroxyl group.⁵⁴⁹

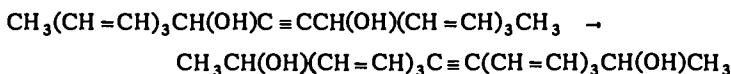
The compounds $RC \equiv CCH(OH)CH = CH_2$ undergo the transformation slowly.

Similar isomerizations have been observed with a wide range of compounds of this type. An oxonium ion of the type of



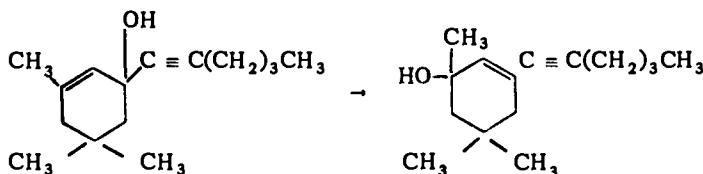
would appear to be an intermediate in the rearrangement, which would seem, therefore, to involve the intramolecular migration of a neutral water molecule. Increasing alkyl substitution increases the rate of isomerization,¹⁸⁹ the compound $CH_3(CH_2)_3C \equiv CC(OH)C(CH_3)CH = C(CH_3)_2$ isomerizing 1.4×10^9 times as rapidly as $CH \equiv CC(OH)CH = CH_2$.

The migration of the hydroxyl group may take place over a series of conjugated ethylenic bonds, migration over as many as three ethylenic bonds having been observed:¹⁹⁰



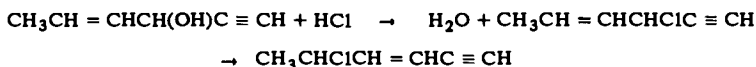
This change takes place under very mild condition, for example, in cold acetone solution of dilute acids.

Rearrangements of the same type have been observed with cyclic unsaturated compounds, an example being provided by the following transformation:

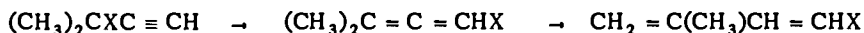


Isomerization takes place under the action of 0.1% sulfuric acid, stronger concentrations causing dehydration.

When acetylenic carbinols of the type $RCH = CHCH(OH)C \equiv CH$ are treated with a cold pyridine solution of hydrogen chloride, they are converted to the corresponding chloride, which rapidly isomerizes through an anionic rearrangement:¹⁹¹



The halo acetylenic compounds of the type $RR'CXC \equiv CH$ in which R and R' are alkyl groups, undergo rearrangement on long standing to halo allenes,¹⁹² and these often undergo further transformation to halo 1,3-butadienes:

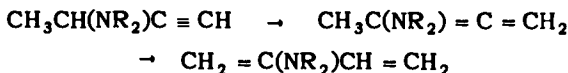


Partial reversion of the halo allene to the original halo acetylene,



occurs on heating with an aqueous suspension of calcium carbonate. These rearrangements take place more readily with the bromo than with the chloro compounds.

An unusual prototropic rearrangement has been observed with 3-amino-1-butyne leading to the formation of 2-aminobutadienes:



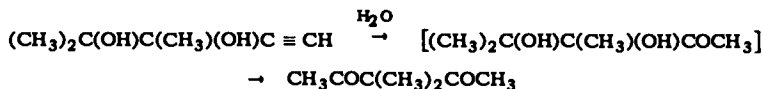
The acetylenic dialdehyde, $\text{OCHCH}(\text{CH}_3)\text{C} \equiv \text{CCH}(\text{CH}_3)\text{CHO}$, has been obtained by the action of 20% sulfuric acid on the erythrol



A pinacol-pinacolone type of rearrangement has been observed with the acetylenic diketo glycol derived from benzil:¹⁹⁴



The transformation takes place under the action of alcoholic hydrogen chloride. This type of rearrangement has been observed to take place during the hydration of a 1-2-acetylenic glycol:¹⁹⁵



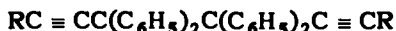
Polymerization of Acetylene

Acetylene may be polymerized by subjecting it to high temperatures, the products being benzene, naphthalene, diphenyl and other aromatic hydrocarbons.¹⁹⁶ Benzene and toluene have been obtained in good yields by the rapid chilling of the products resulting from the heat-polymerization of the compound.¹⁹⁷ Polymerization to the extent of 70% has been achieved by contact with heated active carbon, the resulting mixture consisting of some tarry matter and various products of pyrolysis and polymerization.¹⁹⁸ The condensation of acetylene at 720° in the presence of aluminum chloride gives aromatic bodies in excellent yield. Good conversions have been achieved in a contact time varying between 30 and 100 seconds. The product consists of 50 to 60% benzene, 10 to 15% toluene, ethylbenzenes, xylenes, styrene, 10 to 15% naphthalene, 5 to 10% diphenyl and 5 to 10% anthracene derivatives.

Polymerization of acetylene to benzene may be brought about effectively at 60 to 70° under 15 atm pressure in the presence of the reaction product of nickel carbonyl and triphenylphosphine, $(\text{C}_6\text{H}_5)_3\text{PNi}(\text{CO})_3$ and $[(\text{C}_6\text{H}_5)_3\text{P}]_2\text{Ni}(\text{CO})_2$. These compounds form well defined crystals. They are suitable for the conversion of derivatives of acetylene to aromatic bodies under mild conditions.⁴⁹⁷ These catalysts also induce the copolymerization of acetylene with a substituted ethylene.

The reaction of acetylene with iron carbonyl hydride $\text{Fe}(\text{CO})_4\text{H}_2$ in aqueous solution leads to the formation of hydroquinone.⁵⁵⁰

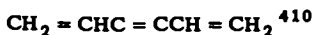
A double bond in the vicinity of the acetylenic bond confers on the latter a greater reactivity. The nature and position of substituent exert a considerable influence on the reactivity of polyynes.



shows a tendency to polymerize at room temperature if R is an aliphatic residue, but is stable if R is aromatic.⁴¹¹ The compound $(RC \equiv C)_3C.C(C \equiv CR)_3$ is polymerized only when heated.

Dichloroacetylene polymerizes much more readily than acetylene. Hexachlorobenzene is formed when an ethereal solution of the compound is heated or exposed to the action of light rays.

Acetylene dimerizes to *vinylacetylene*, $CH_2 = CHC \equiv CH$, when passed through a saturated solution of cuprous chloride-ammonium chloride at 50-75°. ⁴⁹⁸ Conversion per pass is 10 to 30%, and yields are good. A saturated solution of cuprous chloride and guanidine hydrochloride is claimed to give better yields. Vinyl acetylene reacts further with acetylene in the presence of cuprous chloride forming



Divinylacetylene may be obtained by passing acetylene at room temperature into a catalyst prepared from cuprous chloride, ammonium chloride and hydrochloric acid maintained at a pH lower than 6. The solution is allowed to stand for 5 to 7 days, and the product is recovered by distillation. Purification is effected by fractional distillation under vacuum. Divinylacetylene is obtained in 70% yield by this method, together with 10% of the tetramer. The catalyst is prepared by heating on a water bath a mixture of 1000 gm cuprous chloride, 390 gm ammonium chloride, 100 gm copper powder, 30 gm 37% hydrochloric acid and 425 cc water until all the copper goes into solution. The reaction is best carried out in a copper or stainless steel vessel.

Acetylene undergoes a remarkable condensation in certain solvents, notably in tetrahydrofuran, in the presence of nickel cyanide, forming an eight membered

ring compound, *cyclooctatetraene*, $CH = CH(CH = CH)_2CH = CH$.¹⁹⁹

The compound may be prepared in good yield as follows: A 5-liter autoclave is charged with 2 liters of tetrahydrofuran to which are added 20 gm of nickel cyanide and 50 gm of powdered calcium carbide. The air in the autoclave is replaced by nitrogen, the autoclave is heated to 60-70° and a mixture of nitrogen and acetylene under 15-20 atm pressure is forced in. The partial pressure of nitrogen should be 6 atm. The mixture in the autoclave is agitated and acetylene is introduced into the autoclave continuously to maintain the pressure for a period of 48 to 60 hours, after which the contents of the autoclave are discharged and filtered. The filtrate is fractionated under reduced pressure, and the crude cyclooctatetraene obtained is purified by distillation under atmospheric pressure. The compound is obtained in 320 to 400 gm yield, together with 30 to 50 gm of resinous matter and 50 gm of benzene. The average yield is 70% of the theoretical, although yields of 90% have been reported.

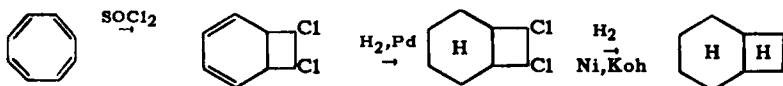
The function of calcium carbide is to eliminate all trace of water from the reaction mixture. This is an important step, since reaction proceeds best under fully anhydrous conditions.

A satisfactory catalyst is obtained by proceeding in the following manner: An

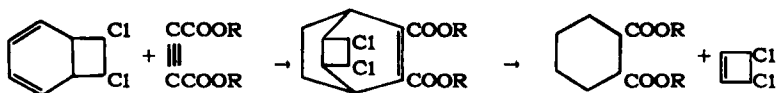
aqueous solution of nickel chloride is cooled to 0 to -10° and 10% aqueous hydrocyanic acid is added with stirring. The mixture is allowed to stand in the cold for twelve hours. A second addition of aqueous hydrocyanic acid is made, and the mass is again allowed to stand for 12 hours. The precipitate is finally filtered, washed to neutral reaction, and is dried to the yellowish-brown anhydrous salt at 175° .

Nickel thiocyanate, the nickel derivative of the enolic form of acetoacetic ester and other enolic compounds, and nickel chloride activated with ethylene oxide are also effective catalysts for the conversion of acetylene to cyclooctatetraene.

Cyclooctatetraene may be chlorinated with sulfuryl chloride to 7,8-dichlorobicyclo-(0,2,4)-octadiene-(2,4), which may be reduced to bicyclo-(0,2,4)-octane by catalytic hydrogenation:

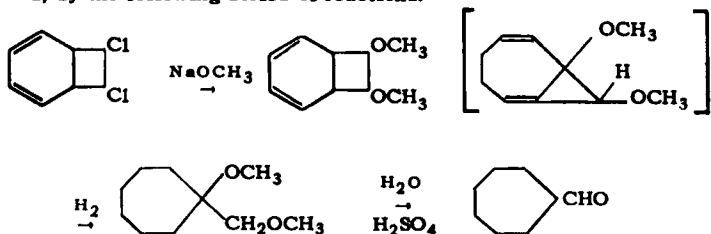


The chloro compound forms an adduct with acetylenedicarboxylic ester which, on heating at 200 to 400° , gives phthalic ester and 1,2-dichlorocyclobutene-3:

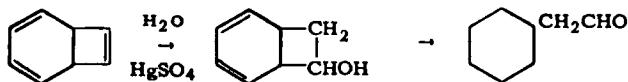


The latter may be catalytically hydrogenated to cyclobutane.

The chloro compound may also be converted to suberanaldehyde, a seven membered ring compound, by the following series of reactions:

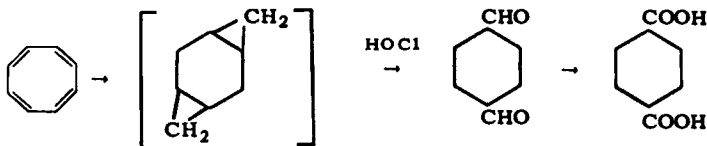


Bicyclo-(0,2,4)-octatriene-(2,4,7) may be converted to phenylacetaldehyde by the action of mercury salts and water:



Phenylacetaldehyde may also be prepared from cyclooctatetraene by conversion to the colorless monoxide by the action of perbenzoic acid, followed by treatment with concentrated sulfuric acid.

The reaction of hypochlorous acid or chromium trioxide with cyclooctatetraene results in the formation of terephthalic acid:



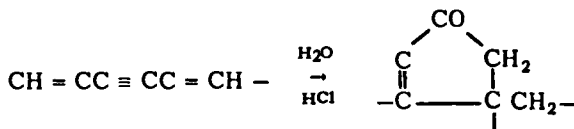
Cyclooctatetraenemonocarboxylic acid is obtained by the carboxylation of cyclooctatetraenelithium.⁴¹²

Alkylated and arylated cyclooctatetraenes have been prepared through the reaction of cyclooctatetraene with metal alkyls and aryls.⁴¹³ The reaction with lithium alkyls has been shown to proceed by addition, followed by the transfer of the equivalent of lithium hydride to another molecule of cyclooctatetraene, with the formation of 1,3,5- and 1,3,6-cyclooctatrienes. 1,3,5-Cyclooctatetraene has been shown to be in equilibrium with the isomeric bicyclooctadiene.⁴¹⁴ Mono and 1,2-disubstituted cyclooctatetraenes have been prepared directly through the copolymerization of mono- and disubstituted acetylenes with acetylene.^{415 486}

Cyclooctatetraene combines with two atoms of lithium. The lithium compound reacts with alcohols to form 1,4,6-cyclooctatriene.

Cyclization of Acetylenic Compounds

Acetylenic compounds of various types are capable of undergoing cyclization. Ring formation may be the result of a condensation involving ethylenic linkages present in the molecule. The formation of cyclic unsaturated ketones from divinylacetylenes in the presence of hydrochloric or other strong acid offers an example of such a cyclization: (*)²⁰⁰

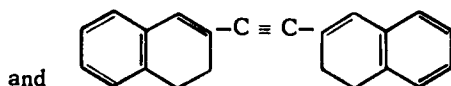
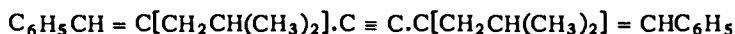


This is known as the *Nazarov cyclization*. There is evidence to show that when hydrogen chloride is used as the condensing agent, a chloro compound, $-\text{HC} = \text{CCCl} = \text{CHC} = \text{CH}-$, is formed as an intermediate and is subsequently hydrolyzed and cyclized to the ring ketone. Good yields are obtained when condensation is effected with hydrochloric acid in the presence of cuprous and ammonium chlorides. The product is sometimes contaminated with chlorinated impurities when hydrogen chloride is used as the condensing agent.²⁰⁰

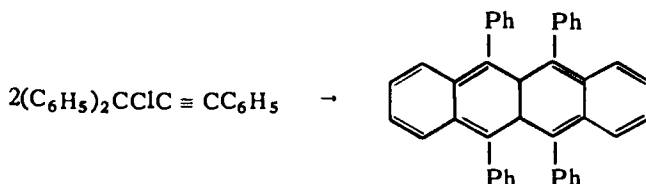
Cyclization fails to occur in this type of compound if one of the double bonds forms part of a benzenoid system. Ring formation occurs only when at least one of the terminal carbon atoms in the diene system carries a hydrogen atom. Polymerization becomes the principal reaction if the diene skeleton carries an insufficient number of substituents.²⁰¹ Cyclization may be accomplished if only one of the ethylenic bonds is conjugated with an aromatic ring,

(*) Marvel, who first studied the reaction, believed that the product of condensation was a six-membered unsaturated ketone; later work showed the fallacy of this view and demonstrated that five-membered rings are formed in the reaction.

but when both double bonds are so conjugated, ring formation does not take place. It is, thus, impossible to cyclize the compounds

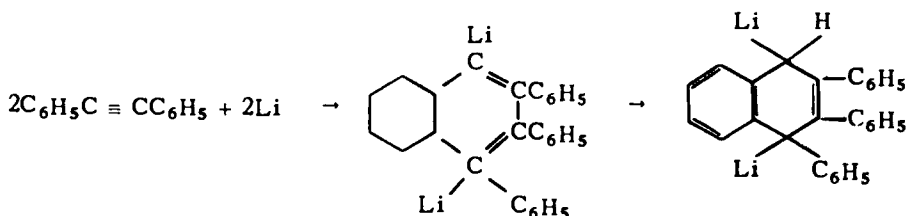


Another type of cyclization involves the union of an aliphatic carbon atom with an aromatic ring through the elimination of hydrogen chloride. **Tetraphenylrubene** results on heating the chloride of diphenyl(phenylethynyl)carbinol under reduced pressure until no further hydrogen chloride is formed.²⁰²

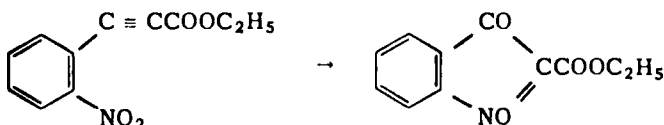


The reaction proceeds at an appreciable rate at room temperature and is strongly exothermic; it results in the formation of considerable proportions of by-products, if it is not carefully regulated. The amount of by-products formed is increased on dilution of the reaction mixture but the addition of 2% quinoline reduces

The cyclization of tolane under the action of alkali metals also involves the acetylenic triple bond:²¹²



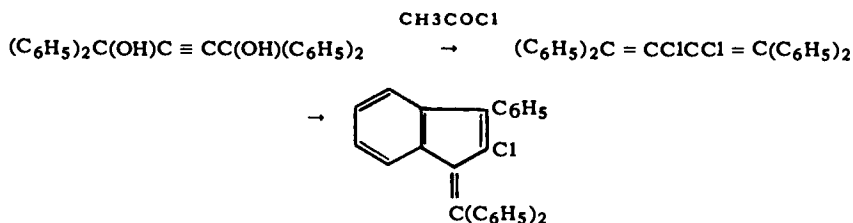
A cyclization of a different type, which also involves the acetylenic bonds, is represented by that of *o*-nitropropionic ester, which isomerizes to isotogenic acid ester under the action of concentrated sulfuric acid:



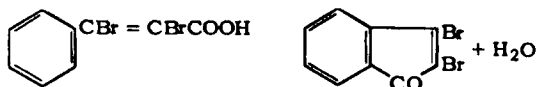
This transformation forms one step in the original synthesis of indigo.

Cyclization occasionally follows hydration of acetylenic carbinols; this occurs when hydroxyl groups are present in the molecule separated by four carbon atoms. Thus, tetramethylbutynediol boiled with an aqueous solution of mercuric

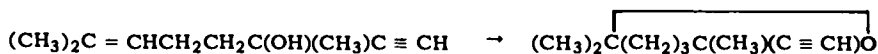
Tetraphenylbutynediol treated with acetyl chloride gives 1-benzhydrylidene-2-chlorophenylindene:²⁰⁸



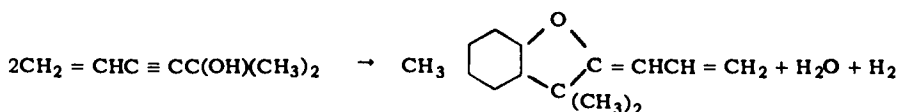
The *cis* form of α,β -dibromocinnamic acids readily cyclize to dibromoindones when treated with sulfuric acid, phosphorus pentoxide, etc.⁴¹⁶



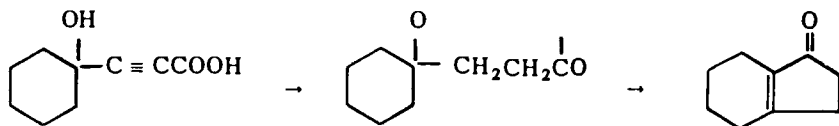
The acetylenic carbinol derived from methylheptenone gives a tetrahydropyran derivative on treatment with formic acid, through an internal condensation involving the hydroxyl group and the ethylenic bond in the compound:²⁰⁹



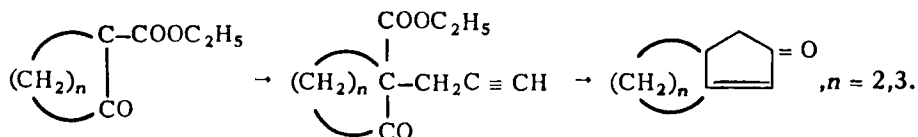
The formation of a vinylisocoumarone from dimethyl vinyl ethynylcarbinol in the presence of formic acid or ferric chloride, on the other hand, is apparently preceded by a molecular rearrangement, and is the result of an internal condensation involving the hydroxyl group and an ethylenic bond as well as an internal Diels-Alder condensation:



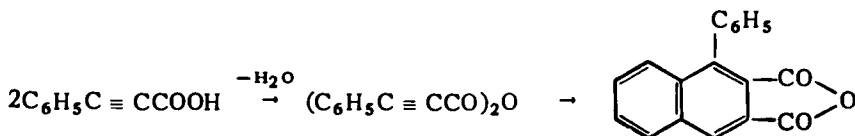
Hydrindones result through the acid catalyzed cyclization of spirolactones formed on complete hydrogenation of the corresponding acetylenic hydroxy acids:⁵²



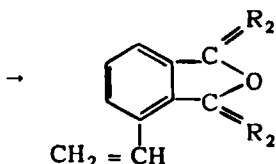
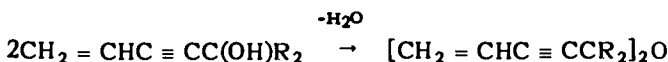
Acetylenic derivatives resulting from the condensation of the sodium compound of cyclohexanone- and cyclopentanone-2-carboxylic acids with propargyl bromide give bicyclic cyclopentanone derivatives on hydration and intramolecular condensation:⁵²⁸



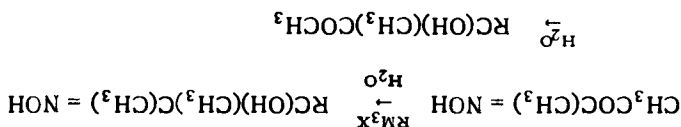
A number of cyclizations have been observed with acetylenic compounds in which the triple bond is directly involved. Typical of such cyclizations is the formation of 3-phenyl-2,3-naphthalenedicarboxylic anhydride from phenylpropionic acid when this compound is treated with acetic anhydride or phosphorus oxychloride:²¹⁰



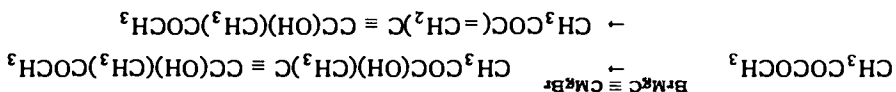
A parallel to this condensation is represented by the formation of tetraalkylvinylisocoumaranes from (vinylethynyl)-dialkylcarbinols in the presence of acids:²¹¹



The reaction of acetylenic Grignard reagents with esters leads to the forma-

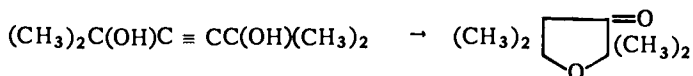


No definite products have been obtained from *tert*-butyl or 1-phenyl-1,2-propanedione. Keto alcohols of the general type $\text{RC}(\text{OH})(\text{CH}_3)\text{COCCH}_3$ have been made by the action of Grignard reagents on methyl isonitrosoethyl ketone, followed by hydrolysis with 10% oxalic acid:



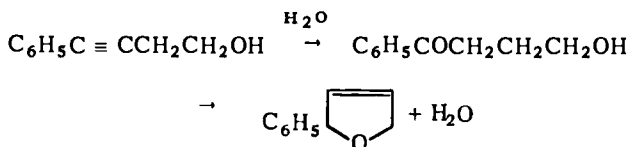
Diketones can, in general, be made to react with one or two equivalents of acetylenic Grignard compounds, giving acetylenic ketols or diacetylenic glycols.²⁵⁴ Only the diacetylenic glycol is obtained, however, with acetonylaceton and many other diketones regardless of the proportion of the ketone and acetylenic Grignard compound used. Diacetyl reacts with only one molecular equivalent of acetylenedimagnesium bromide; the final product of the reaction after hydrolysis of the Grignard complex consists of the expected monoacetylenic glycol, together with its semi-dehydration product:²⁵⁵

chloride until the white precipitate first formed is decomposed, is transformed to tetramethylketotetrahydrofuran:²¹³

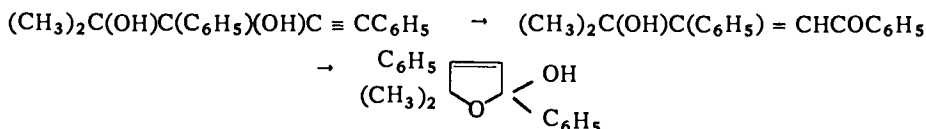


Di(trichloromethyl)butynediol, $\text{Cl}_3\text{CCH}(\text{OH})\text{C} \equiv \text{CCH}(\text{OH})\text{CCl}_3$, is not changed by this treatment, while butynediol and divinylbutynediol undergo oxidation when heated with mercuric chloride solution.

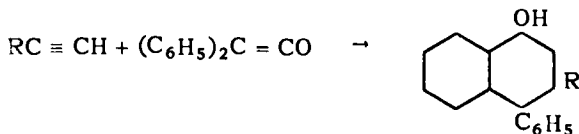
Cyclization may take place also with those acetylenic alcohols which give rise, on hydration, to enolizable keto alcohols in which the carbonyl group is separated from the hydroxyl group by three carbon atoms.²¹⁴ This is the case, for example, with the ketone resulting from phenylethylolacetylene, which cyclizes on heating with aqueous mercuric sulfate to 5-phenyl-2,3-dihydrofuran:



A cyclization of this type may occur also following an intramolecular rearrangement, giving rise to a keto alcohol satisfying the stated condition:²¹⁵

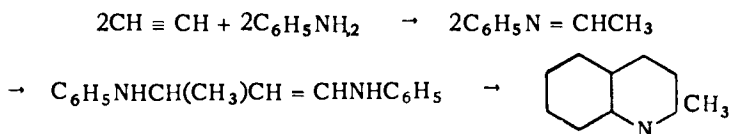


The reaction of aryl acetylenes $\text{RC} \equiv \text{CH}$ with diphenylketene occurs at room temperature in the absence of solvents forming 3-aryl-4-phenyl- α -naphthol in good yield:²¹⁶



Similarly, diphenylacetylene yields 2,3,4-triphenyl- α -naphthol, although the reaction mixture must be heated in this case to 70-80°.

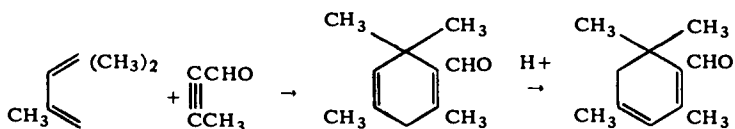
Acetylene heated with primary aromatic amines in the presence of salts of copper and other metals reacts to form quinaldines. The reaction is similar to the Döbner-Miller synthesis and proceeds by a similar mechanism:²¹⁷



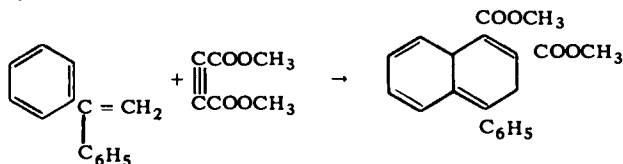
Tetrahydroquinoline and aniline are other products of the condensation.

Cyclic compounds have been prepared through the diene synthesis by use of acetylenic dienophiles.⁵⁵²

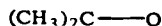
4-Methylsafranin has been synthesized by the diene condensation of 1,1,3-trimethylbutadiene and tetrol aldehyde:⁵⁵³



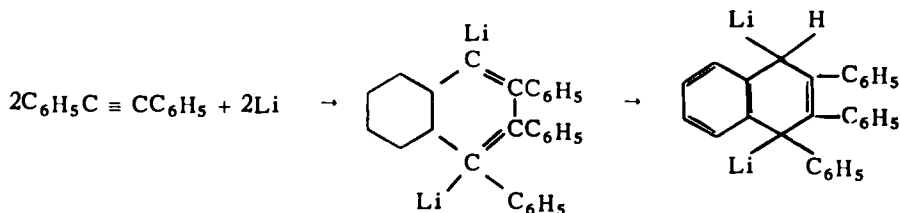
Dihydronaphthalene derivatives have been synthesized from substituted styrenes and acetylenic dienophiles:⁵⁵⁴



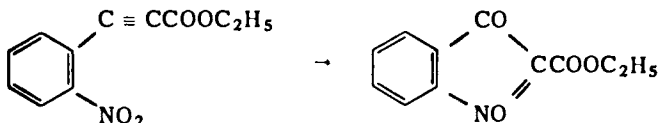
Benzenoid rings have been formed directly through the condensation of vinylacetylenes with acetylenic dienophiles:⁵⁵⁵



The cyclization of tolane under the action of alkali metals also involves the acetylenic triple bond:²¹²



A cyclization of a different type, which also involves the acetylenic bonds, is represented by that of *o*-nitropropionic ester, which isomerizes to isotogenic acid ester under the action of concentrated sulfuric acid:



This transformation forms one step in the original synthesis of indigo.

Cyclization occasionally follows hydration of acetylenic carbinols; this occurs when hydroxyl groups are present in the molecule separated by four carbon atoms. Thus, tetramethylbutynediol boiled with an aqueous solution of mercuric

The reaction with acetylene is generally carried out in ethereal solution at 0° ; the reaction with substituted acetylenes is carried out in anhydrous ether or benzene. With the less reactive ketones, sodium in boiling benzene has been employed.²¹⁹

The method is of wide applicability and has been employed for the preparation of acetylenic alcohols from a great variety of aldehydes and ketones, including formaldehyde. Primary acetylenic alcohols are obtained with polyoxymethylenes.²²⁰ The reaction proceeds well also with alkyl aromatic ketones such as acetophenone, and with cyclic ketones of the type of cyclohexanone. The method has been employed for the preparation of phytol, and of carbinols derived from *trans*-androsterone, 5-*trans*-anhydroandrosterone, and an alcohol related to vitamin A.²²¹

Aldehydes generally give poorer yields of the acetylenic carbinols than ketones. By-products are often formed when the reaction is carried out with enolizable aldehydes and ketones. The method was found to be generally unsatisfactory when applied to unsaturated ketones owing to excessive resinification. Considerable resinification also generally takes place with aldehydes.

The sodium derivative of vinylacetylenes give better results than the potassium or lithium derivatives.²²²

The reaction of carbonyl compounds with sodium acetylides in ethereal solution is often difficult to control, and may result in the formation of several by-products. Yields are usually poor, and occasionally the reaction fails to proceed.²²³

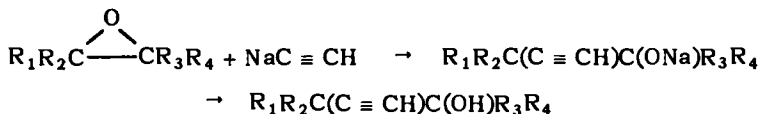
The reaction proceeds better in liquid *ammoniacal* solution,²²⁴ and many ketones of the sex hormone series have been converted to acetylenic carbinols by reaction with potassium acetylide in liquid ammonia. This method is applicable to substituted acetylenes, including vinylacetylene.²²⁵ In preparing the alkali metal acetylide in ammoniacal solution, the metal and acetylenic compound should be introduced at such a rate that no appreciable excess of the metal is present in solution at any time. If this precaution is not observed, a considerable portion of the acetylenic compound is converted by the free metal into the corresponding ethylenic compound. The product is in the form of the sodium salt and the sodium-free compound is liberated by the cautious addition of powdered ammonium chloride three times the weight of the sodium used. In evaporating off the ammonia from solutions of the product a sheet of cellophane tightly drawn over the vessel to act as a cover effectively protects the product from atmospheric moisture without preventing the escape of the vapors of ammonia.

Good yields of the acetylenic carbinols are obtained when the acetylenic compound is made to react with the sodium derivative of the enolic form of the ketone.²²⁶ The ketone is converted to the sodio derivative by reaction with sodamide in cold anhydrous ether. The solution is cooled in ice and acetylene is passed through it at the rate of about 1 lit per minute. The reaction is complete within 3 to 4 hours. The complex formed is hydrolyzed with crushed ice. The carbinol is extracted with ether and is recovered by evaporating off the ether.

In small scale runs lithium acetylide is a more satisfactory reagent since it is more reactive, and reacts more smoothly. The lithium compound affords enhanced yields of acetylenic carbinols from α,β -unsaturated ketones. The reagent may be employed successfully in ethereal suspension.

Sodium acetylide also reacts with alkylene oxides in liquid ammonia to form

the sodium derivative of alkyl carbinols which are converted by hydrolysis to the carbinols:²²⁷



The yield of carbinol decreases markedly with increasing substitution of the oxide.

Triacetylenic carbinols, $(\text{RC} \equiv \text{C})_3\text{COH}$, have been prepared from the sodium derivatives of acetylenic compounds, $\text{RC} \equiv \text{CNa}$, and phosgene.²²⁸

Use of Sodamide as Condensing Agent

A particularly effective method of preparation of acetylenic carbinols from carbonyl compounds makes use of sodamide as a condensing agent. This compound reacts rapidly with acetylene or substituted acetylenes to form their sodium derivatives.

One may proceed by first preparing sodium acetylide through the reaction of the acetylenic compound with sodamide in liquid ammonia solution, subsequently allowing the carbonyl compound to react with the acetylide.²²⁹ Alternatively, the acetylenic compound and the carbonyl compound may be introduced simultaneously into a solution of sodamide in liquid ammonia. The use of sodamide presents the advantage over the use of metallic sodium in that it does not cause the reduction of the acetylenic compound.

The carbinol formed in the reaction is isolated by decomposing the sodio compound with ammonium chloride, allowing the ammonia to evaporate off and finally extracting or distilling the acetylenic alcohol.

Good yields of carbinols can be obtained from saturated carbonyl compounds. The method has been employed satisfactorily in syntheses involving polyene aldehydes and vinylacetylenes.²³⁰ α,β -Unsaturated ketones, which are much less reactive, give good yields of carbinols, provided a large excess of the acetylide is employed.²³¹

The reaction of carbonyl compounds with sodium acetylide, or with acetylene in the presence of sodamide in liquid ammonia does not generally proceed well, but good yields have been reported under certain conditions.²³²

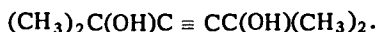
An alternative procedure, depending on the use of sodamide, is to treat an ethereal solution of the carbonyl compound with powdered sodamide and subsequently to add the acetylenic compound. The sodio derivative of the enolic form of the carbonyl compound is first formed, and reacts with the acetylene to form the unsaturated carbinol.²³³

Slight variations in the quantity of sodamide used may lead to varying results. Some ketones fail to react with sodamide, or react very slowly. Furthermore, a number of aldehydes, notably α,β -unsaturated aldehydes, polymerize rapidly in the presence of sodamide.

Carbinols derived from *acetylene* have been prepared by adding two moles of the ketone slowly and with vigorous agitation into a suspension of two moles of sodamide in one liter of ether cooled to -10° , and passing acetylene under 10-15 pounds pressure through the suspension until the evolution of ammonia becomes quite slow. The reaction mixture is maintained at -10° during the passage of acetylene. After completion of the reaction, the mixture is poured into crushed ice, the solution is acidified

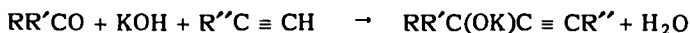
with sulfuric acid, and the carbinol is extracted with ether. The ethereal extract is dried, the solvent is evaporated off, and the carbinol is purified by distillation. The yields range 33 to 50% of theory.

Sym-acetylenic glycols are obtained as by-products in the sodium acetylide-liquid ammonia sodamide method of preparation of acetylenic carbinols. The yield of glycols may be increased by prolonging the reaction time, and by avoiding the use of an excess of acetylene.²³⁴ It may be noted that potassium methylbutynolate, $\text{CH}_3\text{C}(\text{OK})\text{C} \equiv \text{CH}$, kept for some time at 20° , disproportionates to acetylene and the potassium derivative of the acetylene glycol,



Reaction in the Presence of Potassium Hydroxide

The reaction of carbonyl compounds with acetylene in benzene or ether solution proceeds well in the presence of potassium hydroxide, although this method is not applicable to alkali-sensitive carbonyl compounds:²³⁵



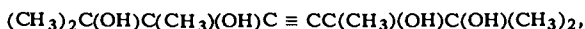
The reaction apparently proceeds in two stages, an addition compound of the carbonyl compound and potassium hydroxide, $\text{RR}'\text{C}(\text{OH})\text{OK}$, being first formed. It will be noted that this reaction bears a resemblance to the addition of chloroform to carbonyl compounds in the presence of potassium hydroxide.

The method is suitable for the large scale preparation of acetylenic carbinols. The reaction is said to proceed successfully in aqueous potassium hydroxide. It has been used successfully for the preparation of tertiary vinyl-acetylenic carbinols.²³⁶

In the reaction of acetone with acetylene under 20 atm gauge pressure, 15% of the acetone is converted to 2-methyl-3-butyn-3-ol, and 20 to 30% to 2,5-dimethyl-3-hexyn-2,5-diol.²³⁷ Similar results are obtained with other ketones. The method is applicable to cyclic ketones, cyclohexanone giving at 85° under 20 atm pressure, 30% of



and 6% of $\text{CH}_2(\text{CH}_2)_4\text{C}(\text{OH})\text{C} \equiv \text{CC}(\text{OH})(\text{CH}_2)_4\text{CH}_2$. The tetrol,



has been prepared in 80% yield from acetylene and acetyl dimethylcarbinol.²³⁸

Ketones react with *calcium carbide* in the presence of potassium hydroxide to form the potassium derivative of an acetylenic alcohol.²³⁹ The reaction is best carried out in solution in an ether or amine or other nitrogen-containing media. It proceeds particularly well in *methylal*, even at low temperatures.²⁴⁰ Other acetals, whether cyclic or acyclic, are suitable media for the reaction.

When powdered potassium hydroxide is heated with an acetal, the solid disintegrates forming a fine suspension, which absorbs acetylene rapidly. When acetone is added to

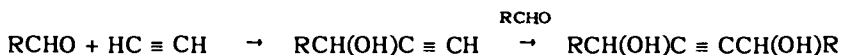
the suspension saturated with acetylene, an exothermic reaction takes place; at -10 to -15° methylbutynol is obtained in almost quantitative yield. The reaction may be carried out by use of ordinary potassium hydroxide, which contains 10-13% of water, providing an excess of the caustic is added. Sodium- and lithium hydroxides cannot replace potassium hydroxide in this reaction.

The acetylenic diol is obtained in good yield when acetylene and the ketone are present in the ratio of 1:2 moles, and the reaction is carried out at 20° . The potassium derivative of the monohydric alcohol is unstable and disproportionates to acetylene and the potassium derivative of the acetylenic glycol when kept for some time.

All ketones react readily, including cyclic ketones such as cyclohexanone, alkyl aromatic ketones, and even ketones of complex structure, as for example, decalone and 3-methyl-1,3-butanol-2-one. Aromatic aldehydes and aldehydes branched at the α -position, such as isobutyraldehyde, also react in a satisfactory manner, but normal aliphatic aldehydes are readily resinified under the action of potassium hydroxide and fail to undergo the reaction.

Reaction in the Presence of Condensing Agents

Acetylenic carbinols and glycols are formed through the reaction of carbonyl compounds with acetylenic hydrocarbons in the presence of acetylides of heavy metals, such as copper, silver, and gold, supported on silica or pumice at elevated temperatures and under pressure:²⁴¹



Acetylene and monosubstituted acetylenes, including amino acetylenes of the type $\text{RR}'\text{NC} \equiv \text{CH}$, undergo the reaction.

The reaction with acetylene is generally carried out at $100-130^{\circ}$ and under a pressure of 5 atm or more. For safe handling, the acetylene is diluted with nitrogen. The method is particularly well suited for the preparation of propargyl alcohol and 2-butyne-4-diol from acetylene and aqueous formaldehyde. These compounds are obtained in yields of up to 90%.²⁴¹ The reaction with formaldehyde is carried out initially at 60 to 70° with a gas mixture containing 10% acetylene, but the temperature is raised toward the end to 100° and the acetylene concentration to 90%. The total reaction time is 12 hours.

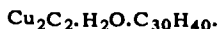
Other aldehydes including acetaldehyde, propionaldehyde, n-butyraldehyde, and isobutyraldehyde also react well. With the higher aldehydes the tendency toward the formation of alkyndiols decreases with increasing molecular weight. Ketones, α,β -unsaturated aldehydes, and aromatic aldehydes also undergo the reaction. Ketones do not give as satisfactory results as aldehydes.

The reaction may be carried out on the commercial scale by the batch method, or continuously. Cuprene formation is one serious difficulty to be overcome when the continuous process is adopted. The formation of this compound is due to the presence of small amounts of metallic copper, and is prevented by the addition of small quantities of mercury or iodine or their compounds. Bismuth trioxide has been used for the purpose, apparently with success. Use of a special alloy steel in parts of the plant through which the liquid passes minimizes cuprene formation.

The catalyst is prepared by repeatedly impregnating and drying silicic acid cast in the form of rods 4-6 mm in diameter and 6-8 mm long and dried at 80° , with a solution of copper and bismuth nitrates in strong nitric acid, and finally heating to $450-550^{\circ}$ in

order to convert the nitrates to oxides. The finished catalyst should contain 12.7% of copper and 3.2% of bismuth.

In use, the copper oxide in the catalyst is converted to copper acetylide which combines with excess acetylene forming a stable addition compound, far less dangerous than free copper acetylide, $\text{Cu}_2\text{C}_2\cdot\text{H}_2\text{O}$. After use for forty successive times, the composition of the addition compound was found to vary from $\text{Cu}_2\text{C}_2\text{H}_2\text{O}\cdot\text{C}_{16}\text{H}_{19}$ to

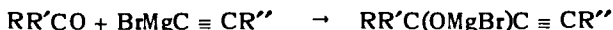
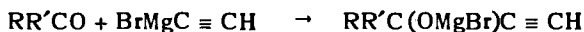


Heated under 5 atm. acetylene pressure, the addition compound decomposes at 251° without explosion.

Sodium ethoxide and other alkali metal alcoholates have been used as condensing agents for the reaction of acetylenic compounds with carbonyl compounds.²⁴² The condensation is shown to be a reversible reaction, and its occurrence, thus, under the action of alkali metal alcoholates, indicates its parallelism with the reaction of carbonyl compounds with hydrocyanic acid, giving rise to cyanhydrins. The method is of fairly general applicability, and has been employed extensively for the preparation of acetylenic glycols from many types of carbonyl compounds. Potassium *tert*-butylate or amylate have been used effectively in special cases,²⁴³ as for example in the preparation of acetylenic carbinols from cyclohexanone and β -ionone.

Preparation of Acetylenic Alcohols by Use of Grignard Reagents

Acetylenic Grignard reagents react with carbonyl compounds to form the halomagnesium derivative of acetylenic carbinols:²⁴⁴



The acetylenic group probably adds as an anion to the carbonyl carbon in this reaction, un-ionized carbonyl compounds such as benzaldehyde and benzophenone giving especially good results.

The mode of procedure may be illustrated by the preparation of 2,7-dimethylocta-1,7-dien-4-yn-3,6-diol from α -methylacraldehyde, $\text{CH}_2 = \text{C}(\text{CH}_3)\text{CHO}$ and acetylenedimagnesium bromide. One liter of benzene is added to a solution of 2 gm of ethylmagnesium bromide in 500 cc ether; the major portion of the ether is distilled off, the solution is cooled and a rapid stream of acetylene is passed for 3 hours with good stirring. Seventy grams of α -methylacraldehyde are now added gradually to the resulting grey suspension in the course of 45 minutes, and the mixture is stirred overnight. The Grignard complex formed is next decomposed by the addition of saturated aqueous ammonium chloride, the benzene layer is washed with water, dried with anhydrous sodium sulfate and evaporated. The viscous residue partly crystallizes when held at 0° for several days. The crystals are freed from the oily matter by washing at 0° with a little benzene, and are recrystallized from benzene, or from a mixture of chloroform and light petroleum. The acetylene used in the reaction is purified by passage successively through acidified copper sulfate solution, chromic acid, concentrated sulfuric acid and phosphorus pentoxide.

The use of aqueous ammonium chloride is preferable to dilute acids in decomposing the final Grignard complex, because in certain cases rearrangements of the resulting

acetylenic alcohol are caused by dilute acids. Any unchanged carbonyl compound may be removed from the reaction mixture as the bisulfite compound or the semicarbazone. Carbinols with a free ethynyl group, $-\text{C} \equiv \text{CH}$, may be isolated and purified in the form of their metal derivatives.

The preparation of monohydric acetylenic alcohols by use of the acetylenic Grignard compounds is not practicable because of the difficulty of preparation of acetylenemonomagnesium bromide, and also because even acetylenemonomagnesium bromide does not give exclusively the monohydric alcohol.²⁴⁵ It is true, however, that one halomagnesium group in acetylene dimagnesium bromide shows a tendency to react preferentially with certain aldehydes, yielding an ethynyl carbinol.²⁴⁶ The method is well adapted for the preparation of *sym*-acetylenic glycols.

Acetylenedimagnesium bromide is prepared conveniently by passing acetylene through an ethereal or benzene solution of ethylmagnesium bromide or iodide at room temperature, until the acetylenic Grignard compound separates out completely as an insoluble, strongly refractive, viscous oil. This is separated and kept in closed vessels. It is not sensitive to shock and does not inflame automatically in contact with air. Crystals begin to separate out of the liquid after storage for three or four weeks; these are probably composed of magnesium carbide and magnesium bromide.

Monohydric acetylenic alcohols have been prepared through the reaction of ethoxyacetylenemagnesium bromide with carbonyl compounds:

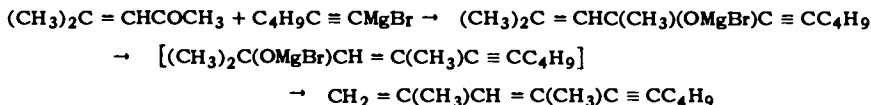


These alcohols undergo hydration to β -hydroxy esters $\text{RR}'\text{C}(\text{OH})\text{CH}_2\text{COOC}_2\text{H}_5$, which may be readily converted to α,β -unsaturated esters, $\text{RR}'\text{C} = \text{CHCOOC}_2\text{H}_5$.⁵⁵⁶

The Grignard method is well adapted to the preparation of carbinols from monosubstituted acetylenes. The method is most apt to lead to positive results in cases not previously described. Satisfactory results are obtained with Grignard compounds derived from vinylacetylene²⁴⁷ and ethynylbutadiene.²⁴⁸

The reaction proceeds satisfactorily both with aldehydes²⁴⁹ and ketones,²⁵⁰ including polyene aldehydes²⁵¹ and α,β -unsaturated ketones, although it proceeds more rapidly with aldehydes than with ketones,²⁵² and the more rapidly the lower the molecular weight of the compound.²⁵³ Grignard compounds derived from vinylacetylene, reacting with paraformaldehyde, give the halomagnesium derivatives of vinylacetylene carbinol. The method has been employed for the synthesis of vitamin A.⁵⁵⁷

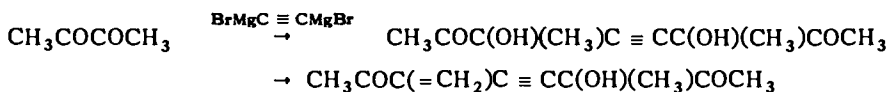
Grignard complexes derived from α,β -unsaturated ketones are often unstable to heat and easily undergo rearrangement accompanied by loss of the elements of water, yielding unsaturated hydrocarbons, as illustrated by the following example:



The product resulting from the reaction of mesityl oxide and vinylacetylenemagnesium bromide, would appear to be the compound $(\text{CH}_2 = \text{C}(\text{CH}_3)\text{CH} = \text{C}(\text{CH}_3)\text{C} \equiv \text{CCH} = \text{CH}_2$, while the reaction of β -benzoylstyrene and α,β -dibenzoylethylene with phenylacetylenemagnesium bromide results only in the formation of resinous products.²⁵⁴

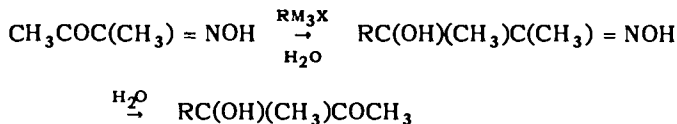
The reaction of acetylenedimagnesium bromide with diphenylketene gives a compound which is probably $(\text{C}_6\text{H}_5)_2\text{CHCOC} \equiv \text{CCOCH}(\text{C}_6\text{H}_5)_2$.²⁵⁵

Diketones can, in general, be made to react with one or two equivalents of acetylenic Grignard compounds, giving acetylenic ketols or diacetylenic glycols.²⁵⁴ Only the diacetylenic glycol is obtained, however, with *acetonylacetone* and many other diketones regardless of the proportion of the ketone and acetylenic Grignard compound used. *Diacetyl* reacts with only one molecular equivalent of acetylenedimagnesium bromide; the final product of the reaction after hydrolysis of the Grignard complex consists of the expected monoacetylenic glycol, together with its semi-dehydration product:²⁵⁵

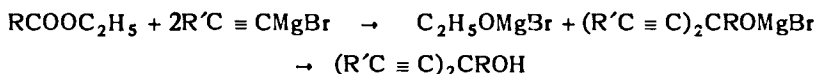


No definite products have been obtained from *furil* or *1-phenyl-1,2-propanedione*.

Keto alcohols of the general type $\text{RC(OH)(CH}_3\text{)COCH}_3$ have been made by the action of Grignard reagents on methyl isonitrosoethyl ketone, followed by hydrolysis with 10% oxalic acid:

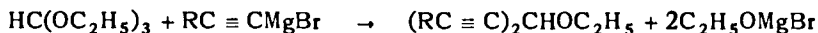


The reaction of acetylenic Grignard reagents with esters leads to the formation of diacetylenic carbinols:²⁵⁷

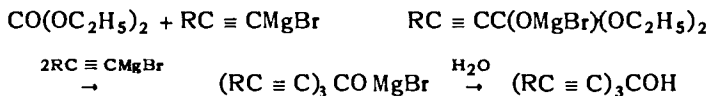


This is the most satisfactory method for the preparation of this type of compound. The reaction proceeds well and the yields are generally greater than 90%, although the expected diethynylcarbinol results in small yield from the reaction of acetylenedimagnesium bromide and formic ester.²⁵⁸

Ethers of diacetylenic carbinols are obtained through the reaction of acetylenic Grignard compounds with orthoformic ester:²⁵⁹



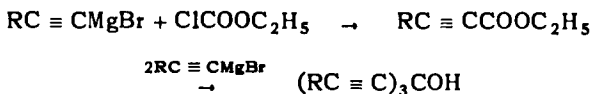
Triacetylenic carbinols result through the reaction of Grignard derivatives of acetylenic compounds with diethyl carbonate:²⁶⁰



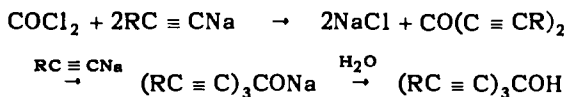
Triacetylenic glycols are obtained in approximately 50% yield. The acetylenic ester, which is formed as an intermediate, may be obtained as the sole product of the reaction when equimolecular proportions of the ester and Grignard compound are used, and is often found as a by-product in the preparation of the triacetylenic carbinol.

Triacetylenic carbinols may also be prepared by the interaction of acetylenic

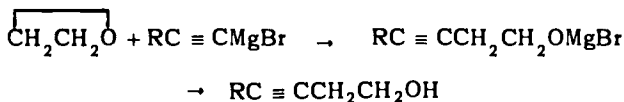
Grignard compounds with ethyl chlorocarbonate.²⁶¹ The initial product of the reaction is an acetylenic ester which reacts further with an excess of the acetylenic reagent to form the halomagnesium derivative of the triacetylenic carbinol:



Triacetylenic carbinols have been further prepared by the reaction of sodium derivatives of acetylenic hydrocarbons with phosgene:²⁶²



Acetylenic alcohols of the type $\text{RC} \equiv \text{CCH}_2\text{CH}_2\text{OH}$ result through the interaction of acetylenic Grignard compounds in anhydrous ether with ethylene oxide:²⁶³



Vinylacetylenemagnesium bromide gives in this reaction 50 to 60% ethylene bromohydrin and only 15 to 25% of the carbinol.²⁶⁴

Miscellaneous Methods

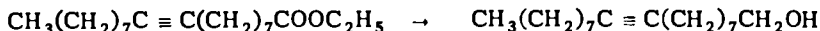
Acetylenic halides may be hydrolyzed to the corresponding alcohols by boiling with an acetone suspension of silver oxide;²⁶⁵ conversion is also often accomplished by boiling with aqueous acetone.²⁶⁶

The result of the treatment of acetylenic halides of the type $\text{RR}'\text{CXC} \equiv \text{CR}''$ with potassium hydroxide varies according to the nature of R, R', and R''.²⁶⁷ If R and R' are aromatic groups and R'' an alkyl group, the halide is fairly stable toward the hydroxide; if R, R', and R'' are all aromatic groups the halide is readily hydrolyzed, while if R and R' are alkyl groups and R'' an aromatic group, a molecule of hydrogen halide is removed, and a substituted vinylacetylene results.

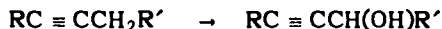
Esters of diphenyl(phenylethynyl) carbinol have been prepared through the reaction of the corresponding chloro compound with the silver salt of a carboxylic acid:²⁶⁸



The Bouveault-Blanc reduction of some acetylenic esters results in the formation of the acetylenic carbinols; this is the case, for example, with stearolic ester:²⁶⁹



Acetylenic hydrocarbons with a methylene group adjacent to the acetylenic carbon are oxidized by *selenium dioxide* to acetylenic carbinols:²⁷⁰



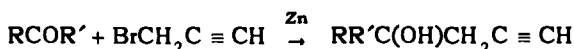
The carbinol $C_6H_5C \equiv CCH(OH)CH_3$ is obtained in 25% yield from phenylethyl-acetylene. Phenylmethylacetylene forms a complex with selenium dioxide which is decomposed by caustic giving 10 to 12% yield of propiophenone.

Acetylenic carbinols are obtained by dehydrobrominating bromovinylcarbinols with potassium hydroxide:²⁷¹



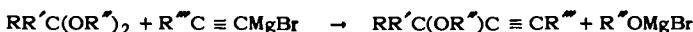
This method is applicable to compounds of the type $CH_2 = CBr(CH_2)_nCH_2OH$, and may serve for the preparation of acetylenic carbinols in which the hydroxyl group is removed from the acetylenic carbon by two or more carbon atoms. The scope of the method is greatly limited because of the inaccessibility and the instability of the required bromovinyl compound.

Propargyl bromide reacts smoothly in the presence of zinc with a variety of saturated carbonyl compounds to form the zinc derivative of acetylenic alcohols, from which the alcohols may be obtained by treatment with acid:⁵⁵⁸



Ethers and Esters of Acetylenic Carbinols

Ethers of acetylenic carbinols result through the reaction of acetylenic Grignard derivatives with alkyl and aryl acetals:²⁷²

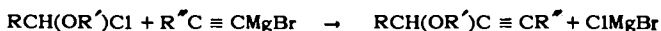


The reaction has been employed for the preparation of ethers of primary, secondary, and tertiary acetylenic carbinols.

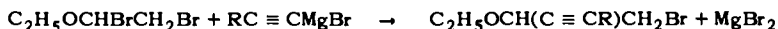
Acetylenic ethers are formed through the reaction of acetylenic acetals with aliphatic and aromatic Grignard compounds:²⁷³



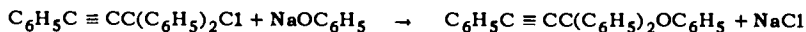
α -Halo ethers react with acetylenic Grignard compounds to form acetylenic ethers:²⁷⁴



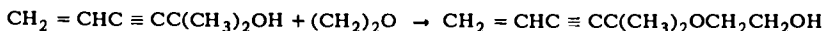
Ethers of acetylenic glycols, $RCH(OR')C \equiv CCH(OR'')R$, are obtained with acetylene dimagnesium bromide.²⁷⁵ Bromo ethers have been obtained similarly through the reaction of acetylenic Grignard reagents with 1,2-dibromoethyl ether:²⁷⁶



Halides of acetylenic carbinols, treated with sodium alcoholates or phenolates, give ethers of the carbinol:²⁷⁷

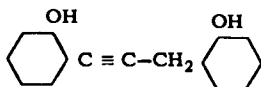


Glycol ethers of vinylacetylenic carbinols have been obtained through the reaction of ethylene oxide with vinylacetylenic carbinols:²⁷⁸

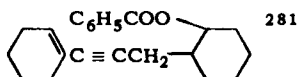


The triple bond in ethoxy- and butoxyacetylene is very readily hydrated.⁴⁸³

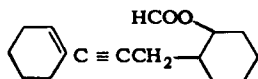
Acetylation of acetylenic carbinols is generally effected by heating with acetic anhydride, usually in the presence of sodium acetate.²⁷⁹ Benzoylation may be carried out in the normal manner.²⁸⁰ Benzoylation of the compound



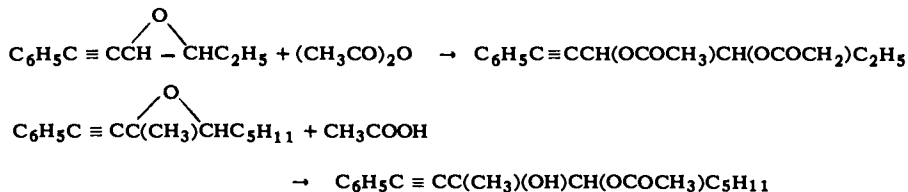
at room temperature, even in the presence of pyridine, results in semi-dehydration with the formation of the monobenzoate



A similar semidehydration is observed when this dihydric alcohol is heated with formic acid, giving the compound

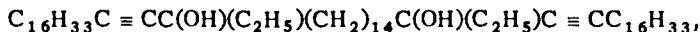


Mono and diacetates of acetylenic glycols are obtained through the reaction of acetylenic oxides with acetic anhydride or acetic acid:²⁸²



Acetylenic Glycols

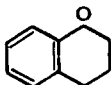
The reaction of acetylenedimagnesium bromide with two molecular equivalents of a carbonyl compound results in the formation of an acetylenic glycol. Dihydric acetylenic alcohols are also formed through the reaction of two molecular equivalents of an acetylenic Grignard compound, $\text{RC} \equiv \text{CMgBr}$, with one molecular equivalent of a diketone.²⁸³ The method has been employed for the preparation of long chain acetylenic glycols, such as



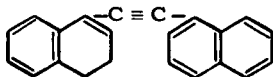
from which the branched-chain hydrocarbon 19,34-diethylpentaconate was derived. Diketoacetylenic glycols are obtained through the reaction of acetylenedimagnesium bromide with diketones, although acetylenic ketols result when equivalent quantities of the ketone and the halomagnesium compound are employed.²⁸⁴

Acetylenic glycols may be prepared also by the reaction of carbonyl compounds with a mixture of calcium carbide and potassium hydroxide.²⁸⁵

The reaction of acetylene dimagnesium bromide with α -tetralone



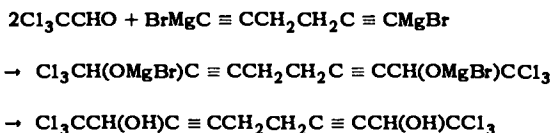
leads to the formation of the unsaturated acetylenic compound



through the spontaneous dehydration of the dihydric alcohol originally formed.²⁸⁶

The reaction of the Grignard compound of diacetylene with aldehydes gives dihydric diacetylene alcohols; it has not been found possible to prepare diacetylenic monohydric alcohols by this method.²⁸⁷ Grignard compounds of diacetylene do not appear to react with formaldehyde and paraformaldehyde.

Diacetylenic glycols may be prepared also from the dihalomagnesium compound of dipropargyl and aldehydes; a dihydric alcohol has been obtained, for example, from chloral:

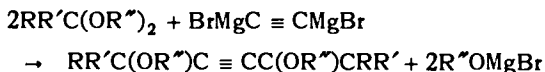


Diacetylenic glycols result through the oxidation of the copper derivatives of acetylenic carbinols of the type of propargyl alcohol with potassium ferricyanide:²⁸⁸



Yields are excellent with *tert*-acetylenic carbinols, but poor with secondary carbinols. Diacetylenic glycols have also been obtained by bubbling air through a mixture of an acetylenic carbinol of the same type with an aqueous solution of cuprous chloride and ammonium chloride.²⁸⁹ The yields are, again, excellent with *tert*-acetylenic carbinols, but poor with *sec*-carbinols.

Diethers of primary, secondary, and tertiary acetylenic glycols result through the reaction of acetylenedimagnesium bromide with acetals and ketals:²⁷²



The acetal of formaldehyde reacts less readily than the acetals of other aldehydes. Ketals react more readily than aliphatic acetals, while benzaldehyde diethyl acetal reacts more readily than ketals.

Behavior and Reactions of Acetylenic Carbinols

Acetylenic carbinols undergo the usual reactions of acetylenic compounds, and in addition some compounds of this class undergo the reactions of unsaturated alcohols.

Halogenation

Chlorination of dimethylethynylcarbinol, $(\text{CH}_3)_2\text{C(OH)C} \equiv \text{CH}$, gives di and tetrachloro addition products.²⁹⁰ In methyl alcoholic solution at 60°, the dichloro keto alcohol $(\text{CH}_3)_2\text{C(OH)COCHCl}_2$ is formed.

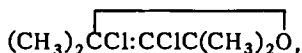
The reaction of bromine with acetylenic carbinols results in the formation of the crystalline dibromides.²⁹¹

The reaction of bromine with acetylenic glycols is less vigorous than with acetylenic hydrocarbons, and generally stops after the addition of one molecular equivalent of the halogen.²⁹² The reaction may be carried out in chloroform solution. The glycol



adds two equivalents of bromine; $\text{C}_6\text{H}_5\text{CH} = \text{CHCH}(\text{OH})\text{C} \equiv \text{CH}$ reacts with three equivalents of the halogen, while $\text{Cl}_3\text{CCH}(\text{OH})\text{C} \equiv \text{CH}$ fails to react, apparently due to steric hindrance.

Halogenation of acetylenic glycols, $\text{RR}'\text{C}(\text{OH})\text{C} \equiv \text{CC}(\text{OH})\text{RR}'$, often results in the formation of dihydrofuran derivatives. Tetramethyldichlorodihydrofuran,

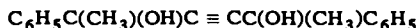


and tetramethyltetrachlorotetrahydrofuran, $(\text{CH}_3)_2\text{CCCl}_2\text{CCl}_2\text{C}(\text{CH}_3)_2\text{O}$, result from the chlorination of $(\text{CH}_3)_2\text{C}(\text{OH})\text{C} \equiv \text{CC}(\text{OH})(\text{CH}_3)_2$;²⁹³ in solution in

aqueous acetone the product is the dichloroketone, $(\text{CH}_3)_2\text{CCOCCl}_2\text{C}(\text{CH}_3)_2\text{O}$. Similar results are obtained with bromine.

The reaction of bromine with ditertiary acetylenic glycols yields dibromodihydro-

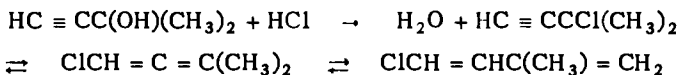
furans;²⁹⁴ tetraphenyldibromodihydrofuran, $(\text{C}_6\text{H}_5)_2\text{CCBr} = \text{CBrC}(\text{C}_6\text{H}_5)_2\text{O}$, is obtained, for example, from $(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\text{C} \equiv \text{CC}(\text{OH})(\text{C}_6\text{H}_5)_2$, reaction proceeding slowly at room temperature, but rapidly at a slightly elevated temperature. The mixed secondary-tertiary glycol $(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\text{C} \equiv \text{CCH}(\text{OH})\text{C}_6\text{H}_5$ also gives the cyclic product. The glycol



gives 90% cyclized product; $(\text{CH}_3)_2\text{C}(\text{OH})\text{C} \equiv \text{CC}(\text{OH})(\text{CH}_3)_2$ 70% of the cyclic product, while the compound $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{C} \equiv \text{CCH}(\text{OH})\text{C}_6\text{H}_5$ yields 60% of the normal addition product, together with a small amount of the cyclic compound.

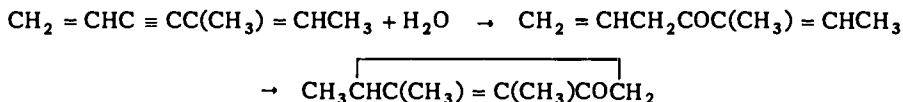
Reaction with Acids

Rapid treatment of ethynylcarbinols with concentrated hydrochloric acid, or dry hydrogen chloride, results in the replacement of the hydroxyl group with chlorine.²⁹⁵ In some cases the reaction proceeds only in the presence of cuprous and ammonium chlorides. The chloro compound undergoes a Meyer-Schuster type rearrangement on long contact with the acid, first to allene, then, slowly, to a conjugated diene:



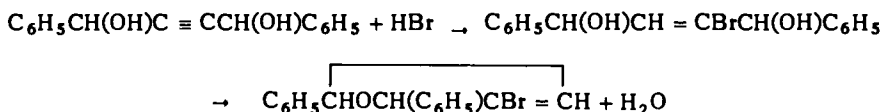
Other tertiary ethynylcarbinols undergo the reaction and isomerization, though at a much slower rate.

3-Methyl-2,6-heptadiene-4-yne treated with concentrated hydrochloric acid is converted to 2,3,4-trimethyl-2-cyclopentenone:²⁹⁶



Other related substituted divinylacetylenes react similarly, the corresponding substituted 2-cyclopentenones being obtained in yields ranging up to 70% of the theoretical.

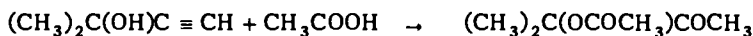
Acetylenic carbinols of the type $\text{RCH}(\text{OH})\text{C} \equiv \text{CCH}(\text{OH})\text{R}$ add halogen acids only if the substituents R are aromatic; the addition products immediately cyclize to dihydrofurans:²⁹⁷



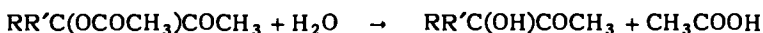
The compound $\text{C}_6\text{H}_5\text{CHBrCH} = \text{CBrCHBrC}_6\text{H}_5$ is also formed in this reaction, which may be carried out in acetic acid solution. The acetylenic carbinol de-

rived from acetophenone similarly gives $\text{C}_6\text{H}_5\text{C}(\text{CH}_3)\text{OC}(\text{CH}_3)(\text{C}_6\text{H}_5)\text{CBr} = \text{CH}$ with hydrogen bromide.

Carboxylic acids react additively with acetylenic carbinols in the presence of boron trifluoride-mercuric oxide or other catalysts.²⁹⁸ The acetate of dimethylacetylcarbinol results from dimethylethynylcarbinol and acetic acid:



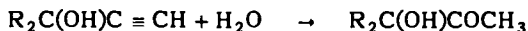
Similar products are obtained with other acids. Acetylenic carbinols derived from formaldehyde and acetaldehyde undergo this reaction. Hydrolysis of the acetoxy ketones obtained results in the formation of acyloins:²⁹⁹



Unstable products result from the reaction of propargyl alcohol, $\text{CH} \equiv \text{CCH}_2\text{OH}$, with carboxylic acids in the presence of catalysts.

Hydration

The direct conversion of acetylenic alcohols into hydroxy ketones is best carried out by use of a mixture of mercuric sulfate and sulfuric acid:³⁰⁰



Carbinols of the type $\text{RC} \equiv \text{CCH}_2\text{OH}$ give $\text{RCOCH}_2\text{CH}_2\text{OH}$. As in all cases of acetylenic bond hydration, no authenticated examples of aldehyde formation are observed.

α,β -Unsaturated ketones are obtained when the hydration is carried out by heating the acetylenic glycol with 90% formic acid, or hydrated oxalic acid.³⁰¹

The hydration of diacetylenic carbinols, $(\text{RC} \equiv \text{C})_2\text{CHOH}$, by use of a 20% alcoholic solution of mercuric chloride results in the formation of α -acetylenic- β -keto alcohols, $\text{RCOCH}_2\text{CH}(\text{OH})\text{C} \equiv \text{CR}$.³⁰² Hydration of both acetylenic bonds is effected by the action

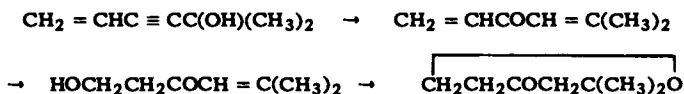
of dilute alcoholic potassium hydroxide solution. These keto compounds are feebly acidic as a result of enolization.

Some vinylacetylenic carbinols of the type $RR'C(OH)C \equiv CCH=CH_2$ are hydrated under the action of a mixture of mercuric sulfate and sulfuric acid and undergo cycliza-

tion to γ -pyranones, $RR'COCH_2CH_2COCH_2$, which are formed in yields up to 60% of theory.³⁰³ This transformation takes place, for example, with the vinylacetylenic carbinol

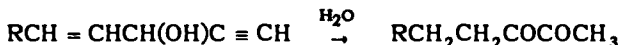


which first undergoes a Meyer-Schuster rearrangement giving a doubly unsaturated ketone, and this is hydrated and finally cyclized:



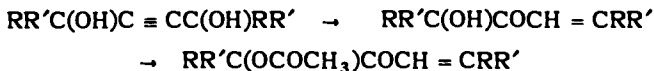
Vinylacetylenic carbinols of the type under consideration derived from diethyl and methyl propyl ketones undergo dehydration to dienes. The corresponding secondary monoalkyl carbinols, $RCH(OH)C \equiv CCH=CH_2$, are readily converted to monoalkyl tetrahydro- γ -pyrones. Substituted divinyl ketones also are converted to pyrone derivatives under the action of acids and mercuric salts or of hydrogen chloride.³⁰⁴

Certain acetylenic carbinols derived from α,β -unsaturated aldehydes give 1,2-diketones on hydration with mercuric sulfate and sulfuric acid:³⁰⁵



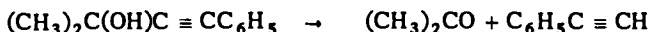
Acetylenic glycols of the type $RR'C(OH)C \equiv CC(OH)RR'$ are converted almost

quantitatively to tetrahydrofuran derivatives, $RR'CCH_2COC(R)(R')O$, when heated with mercuric sulfate.³⁰⁶ Heated with a mixture of acetic anhydride and mercuric oxide, such glycols give α -acetoxyketones in yields ranging up to 45% of theory.³⁰⁷



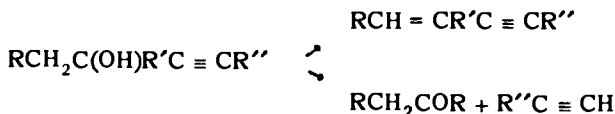
Reaction with Alkalies

Acetylenic carbinols of the type $RR'C(OH)C \equiv CR''$, heated with potassium hydroxide, decompose into the original acetylenic compound and the carbonyl compound from which they were derived:³⁰⁸

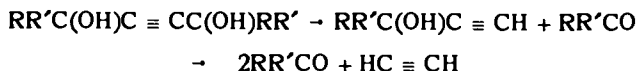


The carbinol $C_6H_5CH(OH)C \equiv CC_6H_5$ polymerizes rapidly on treatment with alcoholic potassium hydroxide.³⁰⁹

Acetylenic glycols are also decomposed on heating with potassium hydroxide,³¹⁰ although the glycol derived from diisopropyl ketone fails to decompose by this treatment. Carbinols of the type $RCH_2C(OH)R'C \equiv CR''$ decompose into ketones or vinylacetylenes when treated with 50 to 60% potassium hydroxide solution:



Acetylenic glycols undergo partial or complete decomposition when heated with potassium carbonate at 150 - 170°;³¹¹



The carbinol is formed almost exclusively when R and R' are alkyl groups, but complete cleavage into acetylene and the carbonyl compound occurs when R and R' are aryl groups.

Cleavage of the carbinols to the acetylenic and carbonyl compounds may be brought about by passing vapors of the carbinol over alumina heated at 230°, the reaction proceeding most readily in the presence of traces of alkalies.³¹² Cleavage occurs to the extent of 50 to 100% with carbinols $\text{RR}'\text{C}(\text{OH})\text{C} \equiv \text{CR}'$, when R is H, CH₃, or C₆H₅, while if R is an alkyl group other than CH₃, the carbinol is dehydrated. The groups R' and R'' have a minor influence on the course of the reaction.³¹³

Ethynyl carbinols derived from high molecular weight ketones, $\text{RR}'\text{C}(\text{OH})\text{C} \equiv \text{CH}$, in which R and R' contain at least 10 carbon atoms are cleaved simply by distillation.³¹⁴ Cleavage of ethynyl carbinols also takes place during hydrogenation in the presence of platinum or palladium catalyst.³¹⁵

Dehydration

Acetylenic carbinols of the type $\text{RCH}_2\text{C}(\text{OH})\text{R}'\text{C} \equiv \text{CR}''$ in which R is an alkyl group, are dehydrated to $\text{RCH} = \text{CR}'\text{C} \equiv \text{CR}''$ when passed over alumina heated to 230°. Cleavage into the carbonyl compound $\text{RCH}_2\text{COR}'$ and the acetylenic compound $\text{R}''\text{C} \equiv \text{CH}$ takes place, however, if R'' is hydrogen or a methyl or phenyl group. Phosphate type catalysts supported on the appropriate carriers are satisfactory for the dehydration of acetylenic carbinols.

3-Butyn-2-ol has been successfully dehydrated to the vinylacetylene,



by passing the vapors of the compound over heated aluminum oxide.

2-Butyn-1,4-diol, $\text{HOCH}_2\text{C} \equiv \text{CCH}_2\text{OH}$, heated with phosphoric acid at 300° under 100 atm pressure, is converted to tetrahydrofuran; the latter is converted to butadiene in contact with certain phosphate catalysts such as alkali hydrogen phosphate or butyl ammonium phosphate at 260-280°.

Some secondary α -hydroxyacetylenes are converted to vinyl acetylenes under the action of potassium bisulfate. An example is the formation of phenylbutylvinylacetylene, $\text{C}_6\text{H}_5\text{CH} = \text{CHC} \equiv \text{CC}_4\text{H}_9$, from $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{OH})\text{C} \equiv \text{CC}_4\text{H}_9$ at 190°.⁵⁵⁹ Conversion of 2,6,6-trimethyl-1-ethynylcyclohexan-1-ol to the corresponding olefinic acetylene has been accomplished by pyrolysis of its acetate.⁵⁶⁰

Tertiary vinylacetylenic carbinols have been successfully dehydrated to homologs of divinylacetylene by means of acetic anhydride containing a trace of sulfuric acid:



Small yields of cumulenes are obtained by the treatment of acetylenic or diacetylenic glycols with P_2I_4 :



The compounds are obtained in somewhat better yield (4%) when the glycols are treated with phosphorus tribromide and pyridine. Diacetylenic glycols in ethereal solution, treated with a reducing agent, such as vanadous or chromous chlorides in the presence of hydrochloric acid, give cumulenes in yields in excess of 90%.³¹⁶ The simplest member of the class, butatriene, has been prepared from 1,4-dibromobut-2-yne by debromination with zinc.⁴⁹⁹

Cumulenes crystallize well from a mixture of acetic acid and chloroform. The properties of tetraphenylhexapentaene may be considered representative of this class of compounds. This compound appears red by transmitted light and imparts to its solutions a cherry red color with a violet tinge. It is remarkably resistant to the action of oxygen. It is destroyed very slowly by a neutral permanganate solution, although it is immediately oxidized by hydrogen peroxide. It may be readily reduced with hydrogen to a compound which gives a negative unsaturation test with tetranitromethane.

Reaction with Alcohols

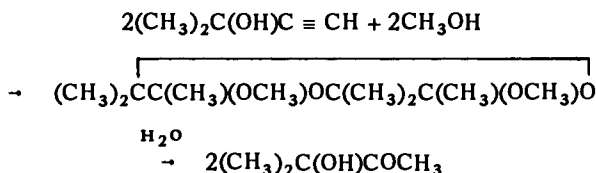
Acetals are obtained through the reaction of alcohols with acetylenic compounds in the presence of mercury salts; hydrolysis of the acetals with dilute sulfuric acid results in the formation of carbonyl compounds, acetaldehyde resulting from acetylene:



Similarly, with dimethylethynylcarbinol a hydroxyacetal is obtained:

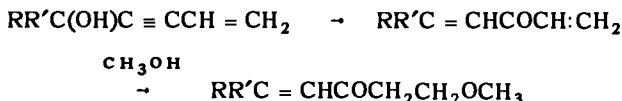


The reaction takes place best in the presence of mercuric oxide activated with boron trifluoride dissolved in ether. Cyclic acetals may be obtained from acetylenic carbinols, and these, on hydrolysis, yield ketols:³¹⁷



Analogous additions take place with other alcohols, provided mercuric oxide activated by trichloroacetic acid is used as a catalyst.

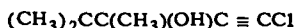
Tertiary vinylacetylenic carbinols are converted to unsaturated methoxy ketones in yields up to 70%, under the action of methyl alcoholic mercuric sulfate:³¹⁸



Miscellaneous Reactions

Methylbutynol and its homologs do not behave toward carboxylic acids in the manner of tertiary alcohols, but readily yield esters. The esters are stable and undergo the reactions of acetylenic compounds in a normal manner.

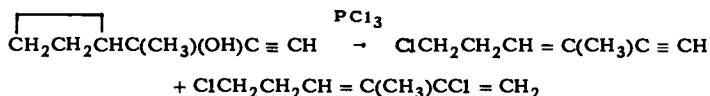
Replacement of the hydroxyl group in the acetylenic carbinol



with chlorine has been accomplished by treatment with a mixture of cuprous chloride and ammonium chloride and concentrated hydrochloric acid for four hours at room temperature.³¹⁹ Contact with the reagent for much longer periods causes isomerization of the acetylenic dichloride to an allene dichloride, $(\text{CH}_3)_3\text{CC}(\text{CH}_3) = \text{C} = \text{CCl}_2$.

Complex reactions may ensue when acetylenic carbinols are treated with phosphorus trichloride.

Thus, cyclopropylethynylcarbinol treated with the trichloride undergoes a ring rupture and dehydration, a portion of the compound also undergoing an addition reaction:³²⁰



Acetylenic oxides are formed from acetylenic carbinols derived from α -chloro aldehydes and ketones and monosubstituted acetylenes, by reaction with conc.

Dehydration

Acetylenic carbinols of the type $\text{RCH}_2\text{C}(\text{OH})\text{R}'\text{C} \equiv \text{CR}''$ in which R is an alkyl group, are dehydrated to $\text{RCH} = \text{CR}'\text{C} \equiv \text{CR}''$ when passed over alumina heated to 230° . Cleavage into the carbonyl compound $\text{RCH}_2\text{COR}'$ and the acetylenic compound $\text{R}''\text{C} \equiv \text{CH}$ takes place, however, if R'' is hydrogen or a methyl or phenyl group. Phosphate type catalysts supported on the appropriate carriers are satisfactory for the dehydration of acetylenic carbinols.

3-Butyn-2-ol has been successfully dehydrated to the vinylacetylene,

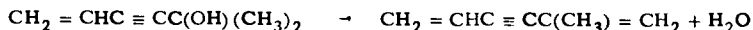


by passing the vapors of the compound over heated aluminum oxide.

2-Butyn-1,4-diol, $\text{HOCH}_2\text{C} \equiv \text{CCH}_2\text{OH}$, heated with phosphoric acid at 300° under 100 atm pressure, is converted to tetrahydrofuran; the latter is converted to butadiene in contact with certain phosphate catalysts such as alkali hydrogen phosphate or butyl ammonium phosphate at 260 – 280° .

Some secondary α -hydroxyacetylenes are converted to vinyl acetylenes under the action of potassium bisulfate. An example is the formation of phenylbutylvinylacetylene, $\text{C}_6\text{H}_5\text{CH} = \text{CHC} \equiv \text{CC}_4\text{H}_9$, from $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{OH})\text{C} \equiv \text{CC}_4\text{H}_9$ at 190° .⁵⁵⁹ Conversion of 2,6,6-trimethyl-1-ethynylcyclohexan-1-ol to the corresponding olefinic acetylene has been accomplished by pyrolysis of its acetate.⁵⁶⁰

Tertiary vinylacetylenic carbinols have been successfully dehydrated to homologs of divinylacetylene by means of acetic anhydride containing a trace of sulfuric acid:



duced by lithium aluminum hydride to the allene alcohol $\text{CH}_2=\text{C}=\text{CHCH}_2\text{CH}_2\text{OH}$ in 60% yield.

Alcohols of the type $\text{RC}\equiv\text{CCH}(\text{OH})\text{CH}=\text{CHCH}_3$, reduced with lithium aluminum hydride, give the diethylenic alcohols $\text{RCH}=\text{CHCH}(\text{OH})\text{CH}=\text{CHCH}_3$, by preferential action on the triple bond in the absence of steric hindrance.⁵⁶¹

Reduction of acetylenic compounds containing the grouping $\text{C}\equiv\text{CCH}_2\text{Br}$ gives the corresponding methylacetylene and not an allene as has been reported erroneously.⁵⁶²

Ethylenic glycols of the type $\text{RR}'\text{C}(\text{OH})\text{CH}=\text{CHC}(\text{OH})\text{RR}'$ are not cleaved at the double bond on oxidation in the gas phase in the presence of catalysts, 2-butenediol, $\text{HOCH}_2\text{CH}=\text{CHCH}_2\text{OH}$, being converted to maleic acid.

Pentahydric sugar alcohols have been synthesized via the acetylenic carbinols and glycols, the synthesis involving semi-hydrogenation of the acetylenic bond over palladium catalyst, and the hydroxylation of the resulting ethylenic compound with silver chlorate-osmium tetroxide mixture.³²⁴ Hexitols have also been prepared similarly.

Acetylenic Carbonyl Compounds

Sodium derivatives of monosubstituted acetylenes condense with ethyl formate in ethereal solution to give the sodium derivative of a half acetal:



Hydrolysis of this half acetal gives an acetylenic aldehyde, $\text{RC}\equiv\text{CCHO}$. A number of homologs of propiolic aldehyde have been prepared by this method.³²⁵ Reaction with orthoformic ester results in the formation of acetylenic acetals:³²⁶



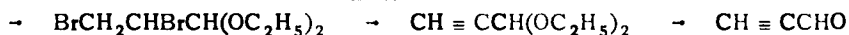
Acetylenic acetals may be synthesized also through the reaction of acetylenic Grignard reagents with orthoformic or chloroformic esters.⁵⁶³

As an example, the preparation of 1,1-diethoxydodecan-2,8-diyne may be cited:⁵⁶⁴ Seventeen grams of undeca-1,7-diyne are added with stirring to a solution of 23 gm of ethylmagnesium bromide in 200 cc ether and the mixture is heated under reflux until the evolution of ethane ceases. A solution of 18 gm of ethyl chloroformate in 20 cc of ether is run in and the mixture is heated for six hours under reflux. The reaction mixture is cooled and hydrolyzed with excess 50% aqueous acetic acid; the ether layer is washed with aqueous sodium carbonate and water, dried with magnesium sulfate and the product is isolated by fractional distillation. The yield of diacetylenic acetal is 21.6 gm, or 82% of theory.

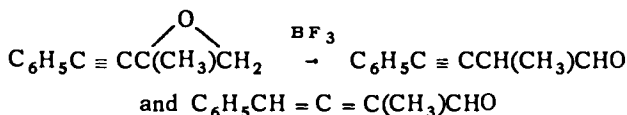
Acetylenic aldehydes may be prepared from olefinic aldehydes by bromination followed by transformation of the dibromoaldehyde to an acetal and the subsequent treatment of the latter with alcoholic potassium hydroxide, hydrolysis of the resulting acetylenic acetal giving the corresponding aldehyde. Propiolic aldehyde has been prepared from acrolein by this method:³²⁷



KOH



Isomerization of acetylenic epoxides, in which the oxygen is joined to an end methylene group, with boron trifluoride yields an acetylenic aldehyde together with an allene aldehyde:⁵⁶⁵



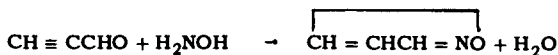
The proportion of the two compounds formed is dependent on the character of the acetylenic epoxide.

Cold dilute aqueous alkalis convert propiolic aldehyde instantly to acetylene and alkali metal formate:

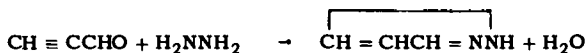


It appears, therefore, that the formyl group is held by the acetylenic group less strongly than the carboxyl group, the latter being cleaved only on long boiling with aqueous alkali.

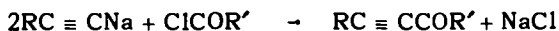
Propiolic aldehyde reacts with hydroxylamine forming isoxazole:⁴¹⁷



pyrazole is obtained by reaction with hydrazine:



Acetylenic ketones result through the reaction of sodium derivatives of mono-substituted acetylenes with acid chlorides:³²⁸

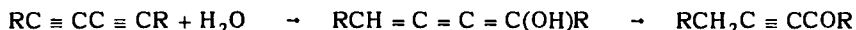


Oenanthylidene methyl ketone, $\text{CH}_3(\text{CH}_2)_4\text{C} \equiv \text{CCOCH}_3$, has been obtained, for example, from oenanthylidene sodium and acetyl chloride.

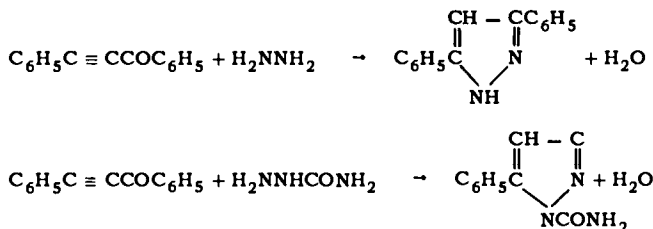
Oxidation of ynols under the proper conditions yields acetylenic ketones. The ymol is dissolved in acetic acid and is treated at 0° with an acetic acid solution of chromium trioxide. Water is then added to the reaction mixture and the ketone formed is extracted with a suitable solvent. The yields are generally very good.⁴¹⁸ A secondary alcohol group situated between a double and triple bond, or between two triple bonds may be oxidized successfully to a carbonyl group. Oxidation of a disubstituted α , α' -dihydroxyacetylene gives the expected diketone; in some instances the intermediate hydroxyketone can be isolated by modifying the conditions.

As an example of the procedure, the preparation of hex-4-en-1-yn-3-one may be mentioned: 250 gm of hex-4-en-1-yn-3-ol in 500 cc acetone are added slowly and with stirring to a cooled solution of 175 gm chromium trioxide in a mixture of 500 cc water and 148 cc sulfuric acid. The operation is carried out in an atmosphere of nitrogen. The rate of addition is so adjusted as to maintain the temperature of the mixture at 5° . Stirring is continued for 30 minutes after the addition of the alcohol, and the mixture is then diluted with water. The ketone is isolated by extraction with ether. The yield is 193 gm.

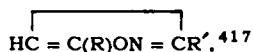
Partial hydration of diynes also yields acetylenic ketones. Hydration is effected by means of sulfuric acid in the absence of mercuric salts.⁴¹⁹ Occasionally a 1,4-addition of the elements of water takes place, followed by re-arrangement into an acetylenic ketone:⁴²⁰



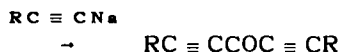
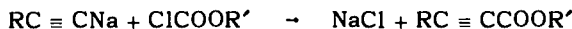
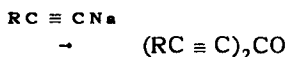
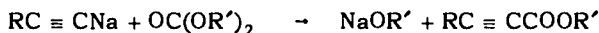
The ketone $C_6H_5C \equiv CCOC_6H_5$ gives cyclic bodies with hydrazine and semi-carbazone:



Hydroxylamine reacts with acetylenic ketones $RC \equiv CCOR'$ to form the isoxazoles

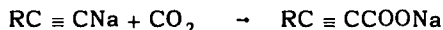


The reaction of halomagnesium acetylides with acetic anhydride also gives ketones.³²⁹ Diacetylenic ketones are obtained when metallic acetylides are made to react with carbonic esters or haloformic esters:³³⁰



Acetylene Carboxylic Acids

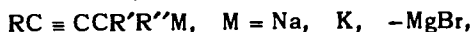
Acetylenic acids result in the form of their sodium salt through the interaction of the sodium derivatives of monosubstituted acetylenic compounds with carbon dioxide.³³¹ Reaction takes place readily when carbon dioxide is conducted through the ethereal or benzene solution of the sodium acetylide:



Sodium propiolate is obtained by this method in 75% yield through the interaction of sodium acetylide with carbon dioxide under 50 to 60 atm pressure.³³² Carbonation may be successfully carried out in liquid ammonia.

Sodium acetylide containing traces of caustic carbonizes with great evolution of heat when subjected to the action of carbon dioxide under pressure. This difficulty is overcome by mixing the acetylide with sand.⁴²¹

Acetylenic acids have been prepared from compounds of the type



by reaction with carbon dioxide.⁴²²

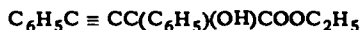
The reaction of the sodium derivative of phenylacetylene with succinic anhydride, $\text{CH}_2\text{CH}_2\text{COOCO}$, results in the formation of the sodium salt of 5-phenyl-3-keto-4-pentyno-1-carboxylic acid, $\text{C}_6\text{H}_5\text{C} \equiv \text{CCO}(\text{CH}_2)_2\text{COOH}$.⁴²³

Carbon dioxide reacts with acetylenic Grignard reagents in ethereal solution to form the halomagnesium salts of acetylenic acids. Acetylene dicarboxylic acid has been obtained by this method in low yield from acetylenedimagnesium bromide:³³³



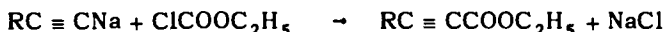
Homologs of propiolic acid have been prepared from halomagnesium derivatives of monosubstituted acetylenes.³³⁵ In the carbonation of acetylenic Grignard reagents yields are often increased when the reaction is carried out under pressure at ordinary temperature. This procedure is most suitable for the carbonation of Grignard compounds derived from ethynyl carbinole.⁵⁶⁶

Purification of acetylenic acids may sometimes be effected by the hydrolysis of acetylenic esters purified by fractional distillation. Hydrolysis must be carried out under mild conditions in order to avoid hydration of the triple bond. The ester



has been successfully hydrolyzed by the action of aqueous sodium hydroxide on a benzene solution of the ester in the cold.⁴²⁴

Esters of primary acetylenic acids have been obtained by the action of chloroformic esters on sodium derivatives of monosubstituted acetylenes:³³⁶



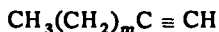
Acetylenic halomagnesium compounds may be employed in the reaction instead of the sodium compound.⁴²⁵ Acetylenic esters also result through the interaction of alkali acetylides or halomagnesium acetylides with carbonic esters:⁴²⁶



Acetylenic acids $\text{HC} \equiv \text{C}(\text{CH}_2)_n\text{COOH}$, in which methylene groups are interposed between the carboxyl and acetylenic group may be prepared by various methods. Acids with one and two methyl groups so interposed have been prepared through the oxidation of the corresponding alcohol with a mixture of chromic and sulfuric acid, a method which is also applicable to the preparation of propiolic acid from the readily available propargyl alcohol.⁵⁶⁷ The reaction of an ω -haloacetylenic compound with malonic ester in the presence of sodium ethoxide is another method employed for the preparation of acetylenic acids of the type $\text{HC} \equiv \text{C}(\text{CH}_2)_n\text{COOH}$. This method has been employed for the preparation of acids with 2 to 5 methylene groups.⁵⁶⁸ This method is not satisfactory for the preparation of δ, ϵ -acetylenic acids, since β -haloacetylenes readily undergo dehydrohalogenation under the conditions of the reaction. Such acids

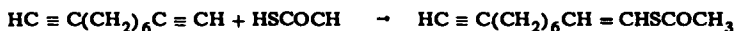
are readily obtained by the reaction of an alkali metal cyanide and γ -chloro-acetylenes, $\text{CH} \equiv \text{C}(\text{CH}_2)_3\text{Cl}$, followed by hydrolysis of the resulting nitrile.⁵⁶⁹

Acetylenic acids $\text{CH}_3(\text{CH}_2)_m\text{C} \equiv \text{C}(\text{CH}_2)_n\text{COOH}$ have been prepared via the nitrile route from the chloro compounds $\text{CH}_3(\text{CH}_2)_m\text{C} \equiv \text{C}(\text{CH}_2)_n\text{Cl}$, which were obtained in turn through the reaction of the acetylenic compounds



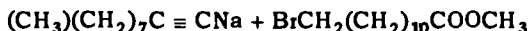
and the halides $\text{I}(\text{CH}_2)_n\text{Cl}$ in the presence of sodamide.⁵⁷⁰ The preparation of the halides $\text{CH}_3(\text{CH}_2)_6\text{C} \equiv \text{C}(\text{CH}_2)_n\text{Cl}$ is carried out satisfactorily by use of the lithium compound $\text{CH}_3(\text{CH}_2)_6\text{C} \equiv \text{CLi}$ in dioxane solution.⁵⁷¹

The diacetylenic acid $\text{CH}_3(\text{CH}_2)_4\text{C} \equiv \text{CCH}_2\text{C} \equiv \text{C}(\text{CH}_2)_7\text{COOH}$ has been prepared from the diacetylene $\text{CH} \equiv \text{C}(\text{CH}_2)_6\text{C} \equiv \text{CH}$ by reaction with thioacetic acid followed by treatment with hydroxylamine to obtain a monoacetylenic oxime:



Conversion of the oxime to aldehyde, then to the glycol acetal; preparation of the Grignard compound of the latter and its reaction with 1-bromooct-2-yne gives the glycol acetal of an aldehyde, from which the aldehyde may be freed by treatment with acid; oxidation of the aldehyde with silver oxide gives the acid in question.⁵⁷²

Acetylenic acids have been obtained in the form of their esters through the interaction of sodio derivatives of acetylenic hydrocarbons with bromo esters:⁴²⁷



Acetylenic acids may be prepared by dehydrohalogenating ethylenic halo acids and acids containing the grouping CH_2CX_2 , X representing a halogen atom:

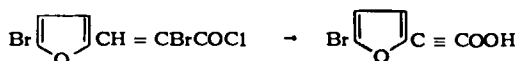


Dihalo acids containing the grouping CH_2CX_2 may be obtained from the corresponding keto acids by treatment with phosphorus pentahalides.

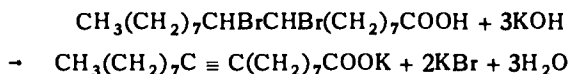
Removal of hydrogen halides is brought about generally with aqueous or alcoholic potassium hydroxide. The temperature at which the reaction is carried out depends on the nature of the halo acid. Some ethylenic acids are decomposed on treatment with caustic, and others suffer rearrangement. Decarboxylation of α,β -acetylenic acids may also occur to some extent. Dehydrohalogenation of α,β -dibromobutyric acid with potassium hydroxide results in the formation of α -methoxycrotonic acid and not of tetrolic acid. Azo derivatives are often formed by the action of hot alcoholic potassium hydroxide on nitrophenylpropionic acid. It is, for this reason, important to carry out the dehydrohalogenation of α,β -dihalo-*p*-nitrophenylpropionic acids at room temperature. It has been observed that the *trans* isomer of haloolefinic acids are more readily dehydrohalogenated than the *cis* isomer.⁴²⁸

While tetrolic acid, $\text{CH}_3\text{C} \equiv \text{CCOOH}$, may be obtained from β -chlorocrotonic acid by treatment with alcoholic caustic, the acid cannot be made from α -chlorocrotonic acid by this treatment. Similarly, phenylpropionic acid may be prepared from β -bromocinnamic acid by the action of alcoholic caustic but not from the α -bromoacid. ⁴²⁹

In the preparation of 5-bromofuryl-2-propionic acid it was found preferable to start with 5-bromofuryl-2- α -bromoacrylic acid chloride, rather the corresponding acid: ⁴³⁰



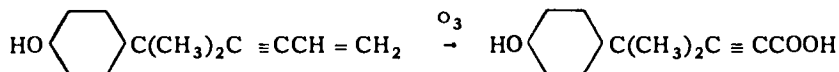
Acetylenic acids may be prepared also from the dibromo addition product of ethylenic acids by dehydrobromination with alcoholic potassium hydroxide. Stearolic acid has been obtained by this method from the dibromide of oleic acid:



Acetylenic acids have been prepared through the rearrangement of conjugated diene acids. ⁴³¹

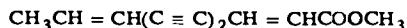
Oxidation of primary acetylenic carbinols leads to the formation of acetylenic acids. ⁴³² Secondary carbinol groups in the molecule are oxidized to carbonyl groups.

Partial ozonolysis of substituted vinyl acetylenes also leads to the formation of acetylenic acids: ⁴³³



Esters of acetylenic acids may be prepared by the direct interaction of the free acids with alcohols in the presence of small quantities of mineral acids. ⁴³⁴ The presence of the triple bond in the molecule exerts a strong retarding influence on the rate of esterification. ⁴³⁵ 2,4-Hexadiyne-1,6-dicarboxylic acid undergoes decomposition. Certain acetylenic acids, such as 4-toluic acid, $(\text{CH} \equiv \text{CCH}_2)_2\text{CHCOOH}$, undergo cyclization under the influence of mineral acids, and esterification of these acids can only be carried out successfully in the cold.

Some acetylenic esters are readily hydrolyzed with caustic. The ester



is hydrolyzed even at 0° with dilute aqueous caustic. ⁴³⁶

Many *acetylenic acid chlorides* may be obtained by the action of phosphorus halides or thionyl chloride on the acids. Thionyl halides are generally considered the most satisfactory reagents since they give halides in better yield, and the by-products are gaseous.

Propiyl chloride cannot be prepared directly from propiolic acid, but the compound has been obtained by the vapor phase pyrolytic dehydrochlorination of α, α -dichloropropionyl chloride at 450° . ⁴³⁷ It polymerizes to a resilient, white solid when allowed to stand in contact with air. Chlorides of homologs of propiolic acid appear to be stable.

The dichloride of acetylenedicarboxylic acid has been prepared by an ingenious application of the Diels-Alder synthesis.⁴³⁸ The acid readily forms an adduct with anthracene; this adduct was converted to the corresponding acyl chloride, and the dichloride of acetylenedicarboxylic acid was subsequently freed by reaction with maleic anhydride.

Very few acetylenic acid *anhydrides* have been prepared. *Propiolic anhydride* has been obtained by the action of phosphorus pentachloride or thionyl chloride on sodium propiolate in ethereal suspension. Behenolic anhydride has been prepared by the action of phosgene on behenolic acid in pyridine solution. *Tribromophenylpropionic anhydride* resulted from the action of acetic anhydride on the acid.

Acetic anhydride converts phenylpropionic acid derivatives to the corresponding 1-phenylnaphthalene-2,3-dicarboxylic anhydrides. 2,4,6-Tribromophenylpropionic acid does not, however, undergo this type of cyclization.⁴³⁹ The anhydride of acetylenedicarboxylic acid is unknown; reactions which would normally lead to the formation of this compound give carbon suboxide, C_3O_2 , and carbon monoxide.⁴³⁸

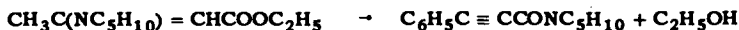
Acetylenic *amides* may be prepared by the usual methods of formation of amides. They may be obtained, for example, through the interaction of ammonia or amines with acetylenic esters or acetylenic acid chlorides.

Amides of acetylenedicarboxylic acid are best prepared through the interaction of this acid with ammonia or amines.⁴⁴⁰ Reaction with aqueous ammonia is carried out at -10° . Some substituted amides of acetylenedicarboxylic acid have been prepared by heating the neutral amine salt of acetylenedicarboxylic acid:⁴⁴¹



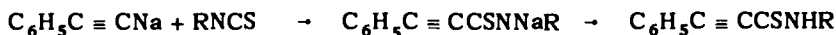
Acetylenic nitriles, $RC \equiv CCN$, have been successfully converted to the corresponding amides by the action of cold concentrated sulfuric acid.⁴⁴² In the case of aromatic α,β -acetylenic nitriles the triple bond is also hydrated, and β -keto amides are obtained.⁴⁴³

β -Piperidinocrotonic ester undergoes rearrangement to tetrolic piperidide when its aqueous solution is evaporated:⁴⁴⁴

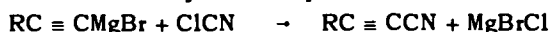


N-Bromophenylpropionic amide, $C_6H_5C \equiv CCONHBr$, results when sodium hypobromite is made to react with propiolic amide.⁴⁴⁵ This bromoamide does not undergo the normal course of the Hofmann degradation, to phenylethynylamine. When phenylpropionic amide is heated with sodium hypochlorite in methanolic solution, benzyl cyanide is formed.⁵⁰⁰

Acetylenic amides have been prepared by the reaction of acetylenic Grignard reagents with isocyanates. Acetylenic *thioamides* have been obtained similarly by the reaction of isothiocyanates with the sodium derivative of acetylenic bodies:⁴⁴⁶



Acetylenic *nitriles* have been prepared by the action of cyanogen chloride on the Grignard derivatives of acetylenic compounds.³³⁷



Certain acetylenic chlorides of the type $RC \equiv C(CH_2)_2CH_2Cl$ have been converted to the corresponding nitriles by the action of alcoholic potassium cyanide.⁴⁴⁷

Dicyanoacetylene, $\text{CNC} \equiv \text{CCN}$, the nitrile corresponding to acetylenedicarboxylic acid, has been prepared by rapidly distilling a mixture of acetylenedicarboxylic diamide, phosphorus pentoxide and sand.⁴⁴⁸ The compound is spontaneously inflammable in air, and its vapors have a powerfully irritant action on the eyes and nose. It is soluble in concentrated sulfuric acid, insoluble in dilute acid. Alkalies decompose dicyanoacetylene with the formation of alkali cyanides and of dark colored products.

Potassium cyanide in aqueous methanolic solution reacts with chloroheptyne to form a cyanoethylenic ether:



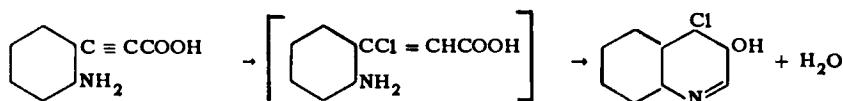
Acetylenic nitriles of the type $\text{RC} \equiv \text{C}(\text{CH}_2)_3\text{CN}$, in which R is $\text{CH}_3(\text{CH}_2)_7$ and C_6H_5 , have been hydrolyzed to the potassium salt of the corresponding acids by the action of 10% alcoholic potassium hydroxide.⁴⁴⁹

Behavior of Acetylenic Acids

Acetylenic acids in which the triple bond is at a distance from the carboxylic group are very stable. In contrast, α,β -acetylenic acids are readily decarboxylated to acetylenic hydrocarbons. The silver salts of the latter are very unstable and lose carbon dioxide, giving the silver compound of the corresponding acetylenic hydrocarbon. Acetylenic acids are much stronger than the corresponding saturated or olefinic acids.

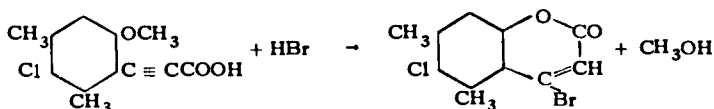
Acetylenic acids are capable of reacting with hydrogen halides to form haloolefinic or saturated dihalo acids.

In many instances secondary changes have been observed in the reaction of aromatic acetylenic acids with hydrogen halides, resulting in the formation of a new ring. α -Aminophenylpropionic acid, for example, yields 4-chloro-2-hydroxyquinoline when subjected to the action of hydrogen chloride:⁴⁵⁰



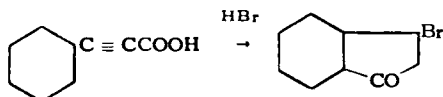
Similar results are obtained with aqueous hydrogen bromide and hydriodic acid, resulting in the formation of the corresponding bromo and iodo hydroxyquinolines.⁴⁵¹

4-Bromo-6-chloro-5,7-dimethylcoumarin results from the reaction of hydrogen bromide with 3-chloro-2,4-dimethyl-6-methoxypropionic acid in acetic acid solution:⁴⁵²

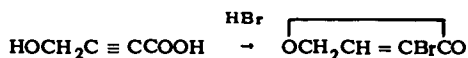


The iodinated derivative is obtained in a similar manner with hydriodic acid.

Phenylpropionic acid condenses to 3-bromoindone under the action of hydrogen bromide:⁴⁵³



Hydroxytetrolac acid yields α -bromo- α,β -butenolactone when treated with hydrogen bromide:⁴⁵⁴



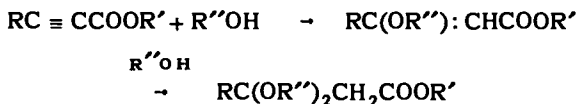
Decarboxylation of certain acetylenic acids takes place by simply boiling the aqueous solution or suspension of the acid. Decarboxylation of α,β -acetylenic acids occurs more readily than that of the corresponding ethylenic or saturated acids.⁴⁵⁵ The heavy metal salts of α,β -acetylenic acids are often more readily decarboxylated than the free acids, and steam distillation of the copper salts offers a convenient method for the decarboxylation of these acids. Decarboxylation of acetylenedicarboxylic acid takes place by warming the ammoniacal solution of many of its heavy metal salts.⁴⁵⁶ Decarboxylation of silver salts often takes place spontaneously at room temperature.⁴⁵⁷ Treatment of the copper salt of aromatic α,β -acetylenic acids with pyridine or quinoline gives the corresponding hydrocarbon, as well as diarylacetylenes.⁴⁵⁸ In most cases loss of carbon dioxide occurs at relatively high temperatures. Secondary changes often occur simultaneously with decarboxylation.

The decarboxylation of acetylenedicarboxylic acid takes place in two stages, acetylenemonocarboxylic acid forming as an intermediate. Acetylenemonocarboxylic acid has been prepared in 46% yield by warming an aqueous solution of the dicarboxylic acid or its potassium salt.⁴⁵⁹

In the reaction of bromine with α,β -acetylenic acids, decarboxylation of the α,β -ethylenic acid formed may take place, especially if the reaction is carried out in aqueous solution.⁴⁶⁰

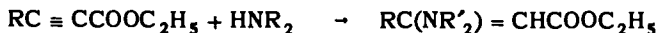
α,β -Acetylenic acids may be readily *hydrated* to β -keto acids by heating with alcoholic alkalis.³³⁸ When aqueous alkalis are employed in this reaction, the keto acids formed break down into carbon dioxide and a methyl ketone.³³⁹ *tert*-Butyl tetrolic acid resists the action of hot alcoholic or aqueous alkalis.

Alcohols react with α,β -acetylenic acids in the presence of sodium alcoholate to form a β -alkoxy- or a β -acetal ester:³⁴⁰



This reaction may be carried out also with alcoholic potassium hydroxide.

Amines also react with α,β -acetylenic acids to form β -aminoacrylic esters:³⁴¹



It has been pointed out that reaction with ammonia leads to the formation of amides, from which acetylenic nitriles may be obtained by dehydration with phosphorus pentoxide.

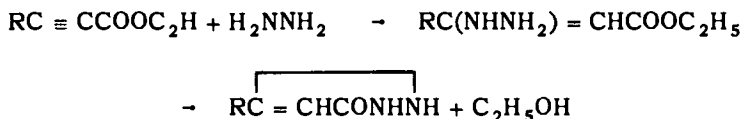
The δ -lactone $\text{CH}_3\text{CHCH}_2\text{C}(\text{OCH}_3) = \text{CHCOO}$ is formed, together with β -methoxy-sorbic acid, $\text{CH}_3\text{CH} = \text{CHC}(\text{OCH}_3) = \text{CHCOOH}$, when the δ -hydroxyacetylenic ester $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{C} \equiv \text{CCOOCH}_3$ is treated with methanolic sodium methoxide. The lactone is formed in 65% yield by the action of the mercuric oxide-boron trifluoride catalyst.⁴⁶²

A γ -lactone $\text{CH}_2(\text{CH}_2)_4\text{CC}(\text{OC}_6\text{H}_5) = \text{CHCOO}$ is formed, together with the hydroxy ester $\text{C}_6\text{H}_{11}(\text{OH})\text{C}(\text{OC}_6\text{H}_5) = \text{CHCOOCH}_3$, when 1-hydroxycyclohexylpropionic ester is heated at 80° with a mixture of phenol and sodium phenoxide. A similar reaction occurs with benzylthiol.

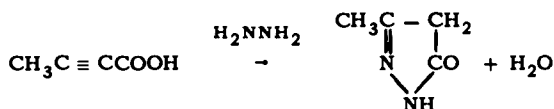
The reaction of amines $\text{R}''\text{R}'''\text{NH}$ with γ -hydroxy esters, $\text{RR}'\text{C}(\text{OH})\text{C} \equiv \text{CCOOAlk}$, results in the formation of the lactones, $\text{RR}'\text{CC}(\text{NR}''\text{R}''') = \text{CHCOO}$.

Hydrobromic acids reacts with acetylenedicarboxylic acid to form monobromofumaric acid.

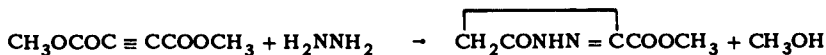
Pyrazolone derivatives are obtained through the reaction of α, β -acetylenic esters with hydrazine:³⁴²



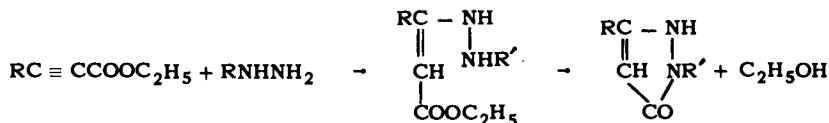
Tetronic acid gives 3-methyl-5-pyrazolone:



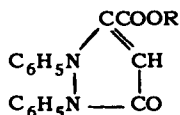
A pyrazolone is formed also with acetylenedicarboxylic ester:⁴⁶³



1,3-Disubstituted-5-pyrazolones are formed readily from aliphatic α, β -acetylenic esters and monosubstituted hydrazine:⁴⁶⁴



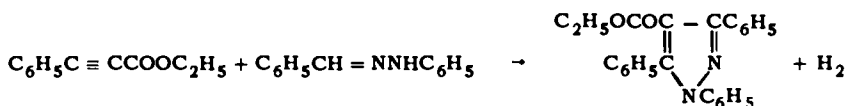
Acetylenedicarboxylic ester, reacting with phenylhydrazine, gives a phenylhydrazone $\text{C}_2\text{H}_5\text{OCOC}(=\text{NNHC}_6\text{H}_5)\text{CH}_2\text{COOC}_2\text{H}_5$. With *sym*-diphenylhydrazine, the primary product is an addition compound, $\text{ROCOC}[\text{N}(\text{C}_6\text{H}_5)\text{NHC}_6\text{H}_5] = \text{CHCOOR}$, which undergoes cyclization to 1,2-diphenyl-5-pyrazolone-3-carboxylic ester



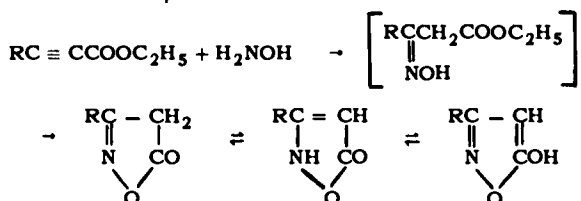
The latter was obtained directly when the reaction was carried out in acetic acid solution, 2,3-Indoledicarboxylic diester was formed on heating the initial condensation product in xylene, and 2-hydroxy-3-anilinocinchoninic acid ester was obtained on heating it with pyridine or dimethylaniline.⁴⁶⁵ A similar primary adduct was obtained from the reaction of acetylenedicarboxylic ester and phenylbenzylhydrazine which, on warming, changed to N-benzoylindole-2,3-dicarboxylic diester.⁴⁶⁶

Arylphenylhydrazones of the type $\text{RCH} = \text{NNHC}_6\text{H}_5$ react with phenylpropionic ester

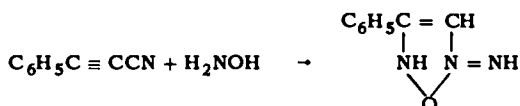
on heating for several hours at 170-180° to form, 1,3,5-triarylpyrazole-4-carboxylic esters,⁴⁶⁷



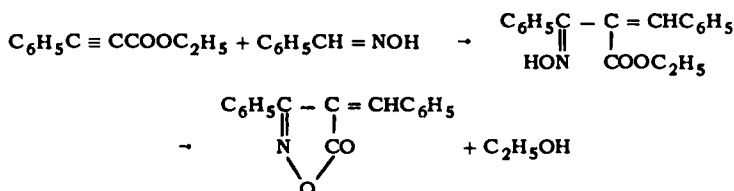
Isoxazolones are formed from α, β -acetylenic esters and hydroxylamine,⁴⁶⁸



Acetylenic nitriles yield isoxazoloneimines:

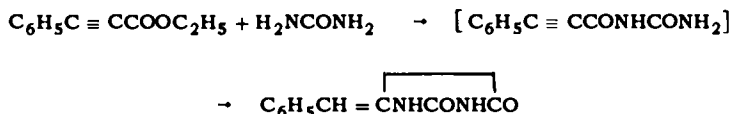


Acetylenic esters react with aldoximes to form arylidene isoxazolones.⁴⁶⁹ Thus, 3-phenyl-4-benzylidene-5-isoxazolone is obtained on heating phenylpropionic ester with benzaldoxime at 140° for an hour:

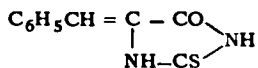


The sodium derivative of benzamide reacts with phenylpropionic acid forming a diketopyrroline. Diketopyrrolines have been obtained similarly from *o*-, *m*- and *p*-toluamides, cinnamamides, anisamide and piperonylamide.⁴⁷⁰

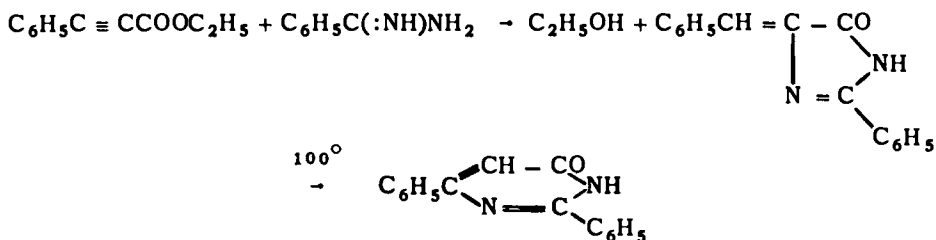
The reaction of urea with phenylpropionic acid in the presence of sodium ethoxide results in the formation of a hydantoin:⁴⁷¹



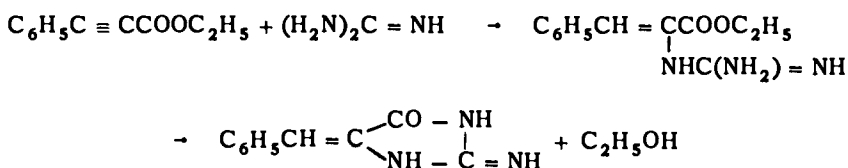
The reaction of monosubstituted ureas with phenylpropionic ester is stated to give open chain products, $\text{C}_6\text{H}_5\text{C} \equiv \text{CCONHCONHR}$.⁴⁷² The reaction of thiourea with phenylpropionic ester is similar to that of urea, and results in the formation of benzalthiohydantoin⁴⁷³



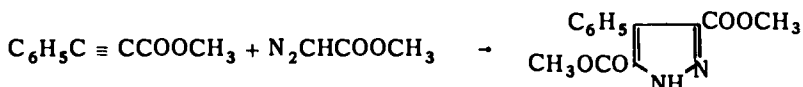
Benzamidine reacting with phenylpropionic ester gives 4(5)-benzal-2-phenyl-5(4)-iminazolone. When the reaction product is heated at 100° some 2,4-diphenyl-6-pyrimidine is formed, together with benzalphenyliminazolone:⁴⁷⁴



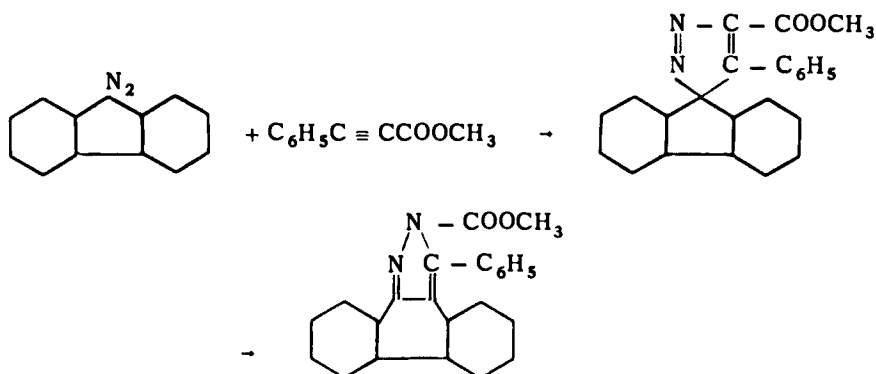
Benzaliminehydantoin results from the reaction of guanidine thiocyanate with phenylpropionic ester:⁴⁷³



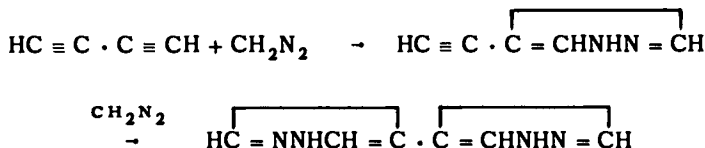
Aliphatic diazo compounds react vigorously with α,β -acetylenic esters giving pyrazole derivatives.⁴⁷⁵ 4-Phenylpyrazole-3,5-dicarboxylic ester results from the reaction of methyl diazoacetate with methyl phenylpropiolate:



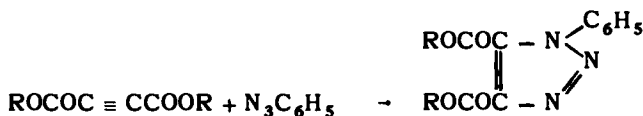
Certain adducts of this type undergo rearrangement when heated with acetic acid;⁴⁷⁶ this occurs with the adduct obtained from diazofluorene and phenylpropionic ester:



Diazomethane allowed to react for one to two days with diacetylene in ethereal solution gives first an acetylenic pyrazole, then a bispyrazole:⁴⁷⁷

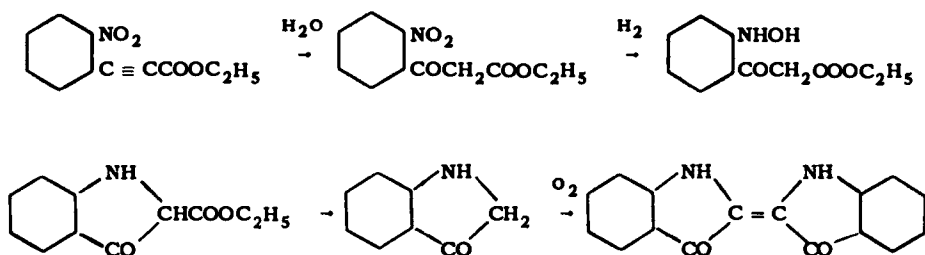


A triazole results from the reaction of phenyl azide with acetylenedicarboxylic ester:⁴⁷⁸

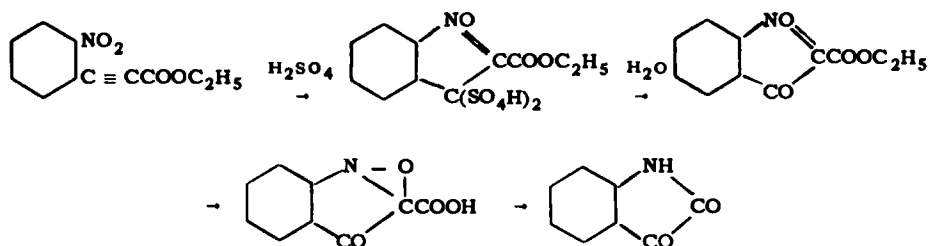


A triazole is formed also from phenylpropionic ester and phenyl azide.

Reduction of *o*-nitrophenylpropionic ester with ammonium sulfide or ferrous sulfate and sulfuric acid results in the formation of indigo.⁴⁷⁹ The reaction involves hydration of the acetylenic bond as the first stage:



o-Nitrophenylpropionic ester, subjected to the action of concentrated sulfuric acid yields isatogenic ester, from which the acid is obtained by hydrolysis. The free acid undergoes rearrangement to isatin:⁴⁸⁰



Cinnolines have been obtained by diazotizing halo-2-aminopropionic acids.³⁵⁴

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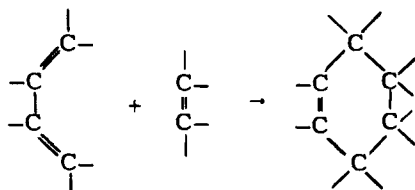
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CHAPTER 20

DIENE SYNTHESIS

The basis of the diene synthesis,¹ also referred to as the *Diels-Alder Synthesis*, is the reaction of a conjugated diene with an unsaturated compound, resulting in a 1,4-addition with the formation of a ring system. The reaction may be represented schematically as follows:



The compounds taking part in the reaction are referred to as the *diene* component and the *dienophile* component. The reaction is not strictly confined to ethylenic compounds, and acetylenic compounds may act either as dienes or dienophiles.

The reaction appears to involve an electron transfer from the diene to the dienophile, the components becoming attached with ionic forces into a temporary complex, and subsequent ionic rearrangements giving rise to the adduct.²

The ability of both the diene component and the dienophile to undergo the reaction varies widely according to the nature of these compounds. The ease with which the reaction proceeds depends on the reactivity of both the diene and dienophile components. With the more reactive pairs, reaction proceeds rapidly at room temperature, while heating for a prolonged period may be required with the less reactive compounds. The reaction is exothermic, the heat effect ranging from 17 to 19Cal per mole.

Procedure

It is often sufficient to bring the components, in the calculated amounts, together in an organic solvent at room temperature, in some instances at -10° , reaction proceeding spontaneously to completion within less than an hour, with almost quantitative yields. Since the reaction is exothermic, provision may have to be made for cooling, especially when large quantities of the reactants are employed. Excellent results are usually obtained if the adduct formed is insoluble in the solvent employed, when it separates out in quantitative yield.

Reaction with cyclopentadiene takes place at room temperature with the following: maleic acid and its anhydride, imide and esters, fumaryl chloride, maleonitrile, fumaronitrile, citraconic and itaconic anhydrides, acrolein, methyl vinyl ketone, phenyl vinyl

ketone, *p*-benzoquinone, α -naphthoquinone, propiolic acid, acetylenedicarboxylic acid and its esters.

In dealing with the less reactive pairs, it becomes necessary to apply heat to the reaction mixture. The optimum temperature varies with the nature of the reactants, and usually ranges between 100 and 170°. The time required for the completion of the reaction also varies with the nature of the reactants. In many instances heating for a period of 10 hours is ample, but in individual instances it may be necessary to heat for 30 hours. Components of low reactivity, which are volatile and are to be subjected to a relatively high temperature, are heated in an autoclave or in a sealed tube.

The solvents usually employed are benzene, toluene, and xylene. The solvent does not affect the direction of the reaction, as a rule, but may greatly influence the rate of reaction.³ The reaction generally proceeds five times as rapidly in polar solvents as in non-polar solvents.⁴

The use of catalysts is not required, although it has been found that certain substances which may act indirectly as donors or acceptors of fragments of molecules without themselves taking part in the diene synthesis, accelerate the reaction. Among such compounds may be mentioned trichloroacetic acid, trimethylamine and probably also dimethylaniline and symmetrical trinitrobenzene.⁵

The diene synthesis has been successfully carried out in an *aqueous emulsion*, the procedure presenting the advantage that the heat of reaction is effectively dissipated by the aqueous vehicle.⁶ A capillary active substance, such as an alkyl-1-naphthalene sulfonic acid, or a sulfuric ester of a higher fatty alcohol, may be employed to advantage in the aqueous emulsion.

The diene reaction is reversible and, for this reason, excessive heating may cause a loss in yield of the adduct. This is clearly indicated in the reaction of cinnamic acid with 2,3-dimethylbutadiene, which, when carried out at 170°, results in a 74% yield of the adduct, but gives a 24% yield when conducted at 240°. Dissociation takes place with varying ease, depending upon the nature of the compounds. Adducts with an *endo* bridge usually show a marked tendency to dissociate.⁷ In many cases the yield of adduct may be improved by employing a large excess of one of the components. Satisfactory results are also achieved when a solvent is employed which holds little or none of the adduct in solution. Immediate chemical transformation of the adduct as it is formed, for example, through dehydrogenation, may also improve the yield by preventing reversal of the reaction.

Many dienes undergo dimerization through a diene condensation involving two molecules of the compound, one of the double bonds in one molecule acting as a dienophile component to give a 1,4-addition product with an other molecule. This type of dimerization is observed, for example, with isoprene, 3,4-dimethyl-2,4-hexadiene, 1,3,5-hexatriene, cyclopentadiene, cyclohexadiene, and diene carboxylic acids.⁸ The tendency toward dimerization is so strong in some dienes that they instantly dimerize at the time of their formation, and they have not been isolated in the monomeric form. This is the case with a number of cyclohexadiene derivatives. Dienes with doubly substituted carbon atoms in the terminal position of the conjugated system are very apt to polymerize.

Thus, 4-methyl-1,3-pentadiene; 4-methyl-, 4-methyl-6-phenyl-, 4-methyl-6-*n*-methoxyphenyl- and 4-*n*-propyl-1,3-hexadienes; 2-methyl- and 2,5-dimethyl-2,4-hexadienes yield polymeric products when an attempt is made to condense these compounds with maleic anhydride.

Conjugated aromatic dienes such as styrene, *p*-methoxy- and 1,4-methylenedioxy-styrenes, anethole, the ethyl ether of *trans*-isoeugenol, stilbene, 1,4-diphenylbutene, benzalfluorene, 5-vinyl- and 5-isopropenylhydrindenes, 1-vinyl- and 1-vinyl-6-methoxynaphthalenes and isopropenylchrysene also give polymeric products when heated with maleic anhydride.

In reactions with maleic anhydride, free maleic acid may cause isomerization of the diene and may thus alter the course of the reaction. Maleic acid may also initiate or accelerate the chain polymerization of the diene.⁹

Chain polymerization, which may be promoted by various agents, may be effectively suppressed by the use of inhibitors such as hydroquinone, amines, phenols, copper salts, metallic copper, etc. It may also be minimized by lowering the reaction temperature, and by the proper choice of the solvent.¹⁰ Methylene blue is stated to be effective in preventing the formation of mixed polymers. The use of inhibitors of polymerization does not prevent dimerization due to diene type reaction between the molecules of the diene.

Aromatization of Adducts by Partial Oxidation

It is occasionally desirable to aromatize the adduct, as it is formed, by partial oxidation. This may often be accomplished by using nitrobenzene as a solvent¹¹ and carrying out the condensation in the temperature range 200-250°. It would appear that nitrobenzene is most effective in its dehydrogenating action with compounds capable of double *ortho* enolization. Thus, adducts of maleic anhydride and quinone are readily dehydrogenated by hot nitrobenzene, while those of cinnamic or crotonic acids and quinones are not.¹² It should be noted, however, that the adduct of indene and methyleneanthrone is aromatized by nitrobenzene to an indenebenzanthrone.¹³ The determining factor is perhaps the inherent tendency of the adduct toward the formation of a stable ring system. Aromatization of adducts of quinones may also be brought about by passing air through the alkaline solution of the adduct.

Diene Analysis

The amount of an active diene in a given sample may be determined by reaction of a weighed quantity of the sample with excess of maleic anhydride, and determination of the quantity of anhydride in excess after completion of the reaction.¹⁴

The procedure generally employed is as follows: One-tenth of a gram of the sample to be analyzed is heated in a sealed tube for 20 hours at 100° with a known excess of maleic anhydride dissolved in acetone. The quantity of maleic anhydride remaining unreacted after the completion of the reaction is determined by one of two methods: The mixture is extracted with water and the filtered extract is titrated with standard alkali. Or, an excess of a mixture of potassium iodide and iodate is added to the reaction product, and the iodine liberated is determined by titration with standard thiosulfate solution. Two equivalents of thiosulfate are required per mole of excess of maleic anhydride used.

The diene content of a given sample is conveniently expressed as the *diene number* which is defined as the quantity $1.269 \times \frac{V}{W}$, in which *V* represents the

volume of $N/10$ alkali required for the neutralization of the portion of the maleic anhydride which reacts with the diene in the sample taken, and W is the weight of the sample in grams.

DIENES AND DIENOPHILE COMPONENTS

General Considerations

It has been pointed out that the readiness with which a diene condensation proceeds depends upon the reactivity of both the diene and dienophile components. The reactivity of either the diene or dienophile is dependent upon their structure and the character of the groups present in their molecule.

Butadiene, $\text{CH}_2 = \text{CHCH} = \text{CH}_2$, simplest of conjugated dienes, is capable of acting as a diene component and combines with many dienophiles. Almost all homologs and analogs of butadiene are also capable of undergoing the diene synthesis, although derivatives of butadiene with large substituents in the 2 and 3 positions are unreactive. Phenyl groups in these positions do not exert a decided effect and a normal behavior is shown by 2,3-diphenylbutadiene.

Alkyl, alkoxy and aryl groups attached at 2 or 2 and 3 positions generally enhance the reactivity of the diene, whereas the presence of these groups at the terminal positions decreases the reactivity.

Five- and six-membered carbon rings containing conjugated double bonds are reactive dienes, and their reactivity is not influenced to any great extent by substituents. They give good yields of adducts with most dienophiles.

Furans fail to react at room temperature with such dienophiles as crotonaldehyde and methyl vinyl ketone, although rapid reaction has been observed with other dienophiles.

Styrene and similar acyclic-aromatic dienes show reduced activity and react with dienophiles only at high temperatures.

Ethylenic dienophiles usually give better yields of adducts than the analogous acetylenic dienophiles; bifunctional dienophiles react more readily than the unifunctional. α,β -Unsaturated acids usually react more readily than their esters.

Ethylene, propylene and other homologs of ethylene may react as dienophiles, although reaction proceeds too slowly to be of preparative value.¹⁵ Activation of the ethylenic bond is caused by certain groups attached to the unsaturated carbon atoms.¹⁶ Carbonyl, carboxyl and cyano groups exert an activating effect. Unsaturated groups and aromatic radicals also have an activating influence. Activated dienophiles of this type have a common characteristic: The unsaturated bonds of the dienophile group are conjugated with the multiple bonds in the activating groups. The effect of multiple linkage may, however, be transmitted through intervening atoms, vinyl acetate, $\text{CH}_2 = \text{CHOCOCH}_3$, reacting, for example, to some extent with butadiene at 180° .¹⁷

The diene addition generally takes place in such a manner that the resulting compounds do not possess angular, geminal or spirane groupings attached to a

carbon atom originally forming part of the unsaturated system of the diene or dienophile.

DIENES

Dienes may be broadly classified as *acyclic*, including open chain conjugated dienes and polyenes; *alicyclic* conjugates with five, six, seven, etc. members in the ring including bicyclic systems; *aromatic* conjugates, including fully aromatic systems, and *heterocyclic* dienes, including furans, isobenzofurans and α -pyrones.

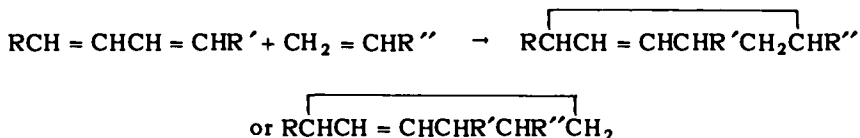
Acyclic Dienes

Among acyclic dienes, *butadiene* and its homologs are generally reactive. Butadiene, for example, reacts readily with maleic anhydride in benzene solution at 100° to give a quantitative yield of the adduct. Substitution on three adjacent carbon atoms would appear to cause a marked inhibition of reactivity, although 4,5-diphenyl-1,2,3,6-tetrahydrophthalic anhydride may be obtained in quantitative yield from 2,3-diphenylbutadiene and maleic anhydride. 1,2,3,4-Tetraphenylbutadiene and 2,2-*tert*-butylbutadiene fail to react;¹⁸ 1,4-di-*p*-anisyl- and 1,4-diphenylenebutadiene also are unreactive toward maleic anhydride.¹⁹

When an unsymmetrically substituted butadiene, such as



undergoes the diene reaction with a dienophile of the type $\text{CH}_2 = \text{CHR}''$, the possibility of the formation of two distinct isomeric adducts exists:



In this example, when R is a phenyl group and R' is a methyl group, the adduct with the substituent R'' in the *ortho* position with respect to the phenyl group predominates. The carboxyl group also exerts a greater effect than the methyl group, the adduct with the substituent in the *ortho* position with respect to the carboxyl group predominating in the reaction mixture. It has been observed, however, that when acrylic acid chloride is condensed with sorbic acid, the adduct in which the COCl group is in the *ortho* position with respect to the methyl group predominates in the product.

In the reaction of $\text{CH}_2 = \text{CRCH} = \text{CH}_2$ with $\text{CH}_2 = \text{CHR}'$ the formation of two isomers is possible. Addition in this case takes place in such a manner that R' is in the *para* position with respect to R in the six-membered ring formed.²⁰ The dimerization of isoprene proceeds in accordance with this rule at high temperatures, but addition takes place in the reverse direction at lower temper-

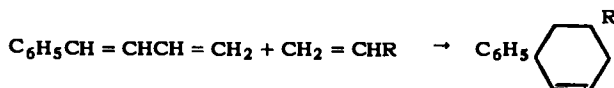
atures. When the substituent R is in 1-position in butadiene, addition takes place in such a manner that R' is in *ortho* position with respect to R.

The reaction between isoprene and methyl vinyl ketone proceeds readily to give

methyl cyclohexene ketone, $\text{CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{CHCOCH}_3$. Similar reactions have been employed for the preparation of compounds which have formed the starting point for the synthesis of compounds of the p-menthan series. Thus, α -terpineol has

been prepared from the ketone $\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CHCOCH}_3$ by reaction with methylmagnesium iodide followed by hydrolysis.

1-Phenylbutadiene reacting with dienophiles gives derivatives of biphenyl:



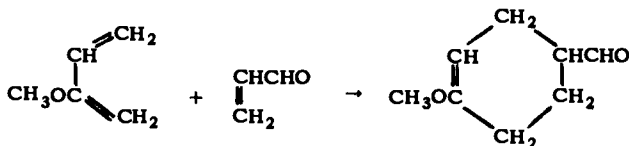
These compounds may be aromatized by heating with selenium.

Butadiene derivatives carrying carboxyl groups, such as sorbic acid,



and muconic acid, $\text{HOCOCH}=\text{CHCH}=\text{CHCOOH}$, are reactive dienes, although dehydrogeranic acid, $(\text{CH}_3)_2\text{CHCH}=\text{CHC}(\text{CH}_3)=\text{CHCOOH}$, could not be condensed with maleic anhydride.²¹ Other butadiene derivatives with negative substituents, such as 1-acetoxybutadiene, $\text{CH}_2=\text{CHCH}=\text{CHOCOCH}_3$, 2-acetoxybutadiene, 1- and 2-alkoxybutadienes, and 1-diethyaminobutadiene are reactive dienes.

2-Alkoxybutadienes react readily with various dienophiles. The optimal conditions are heating in benzene solution in an autoclave at 140 to 160° for 30 to 45 minutes. The yields are generally 70 to 90% of the theoretical. The reaction with acrolein results in the formation of an alkoxy-cyclohexene aldehyde:



hydrolysis with dilute sulfuric acid giving a ketocyclohexyl aldehyde.

2-Alkoxybutadienes may be prepared by treating butadiene with alkylhypobromites, which are in turn prepared through the reaction of benzenesulfodibromamide,



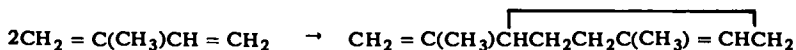
with alcohols.

2-Ethoxybutadiene and 2,3-dimethylbutadiene have been added to 3,4-dihydro-1-naphthoic ester and to its 7-methoxy and 5-bromo-7,8-dimethoxy derivatives.²²

Amino butadienes, $\text{R}_2\text{NCH}=\text{CHCH}=\text{CH}_2$, have served for the preparation of dihydrobenzene derivatives,²³ and higher quinones, the adducts first formed being deaminated for the purpose.

2-Chloro butadienes bearing no other halogen atoms usually add dienophiles, while 1-chloro and 2,3-dichloro butadienes fail to react.

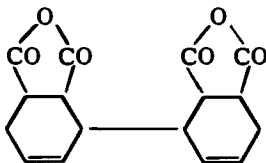
The self-condensation of butadiene derivatives to derivatives of cyclohexane is of interest; isoprene, for example, yields dipentene:



It is possible to condense many butadiene derivatives to cyclohexene derivatives in this manner, but other reactions which follow the original dimerization seriously decrease the yields and make difficult the isolation and purification of the compounds formed.²¹ Since dimerization proceeds only at elevated temperatures, chain polymerization may accompany the reaction. Chain polymerization may be avoided by the addition of inhibitors.

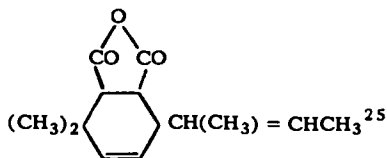
1-Phenylbutadiene appears to dimerize abnormally giving 1-(β -styryl)-2-benzyl-3-cyclopentene.²²

Indications are that with *polyenes* addition takes place at the 1,4-positions, irrespective of the length of the conjugated system, and that each pair of conjugated double bonds in the system acts as an independent unit.²⁴ Thus, two molecular equivalents of maleic anhydride are capable of reacting with 1,3,5,7-octatetraene forming 1,2,3,4,1',2',3',4'-octahydro-2,3,2',3'-tetracarboxydiphenyl-dianhydride,



The adduct of 1,3,5-hexatriene and maleic anhydride is probably 3-vinyl-1,2,3,6-tetrahydrophthalic anhydride.²²

Alloocymene, $(\text{CH}_3)_2\text{C} = \text{CHCH} = \text{CHC}(\text{CH}_3) = \text{CHCH}_3$, adds maleic anhydride, giving a product of the probable structure



2,5-Dimethyl-1,3,5-hexatriene adds maleic anhydride, giving the expected 1,2,3,6-tetrahydro-4-methyl-6-isopropenylphthalic anhydride.²⁶

Dyes of the *bixin* and *carotene* series add maleic anhydride.²⁷ *Vitamin A*²⁸ and *Vitamin D*₂²⁹ (calciferol) also give adducts with maleic anhydride, the former reacting much more readily than the latter.

Octadeca-9,11-dienoic acid, which is a dehydration product of ricinoleic acid, adds dienophiles readily. *Licanic* and *eleostearic acids* form adducts with maleic anhydride when heated at 100° with this compound in benzene solution.³⁰ α -Eleostearic acid yields 6-*n*-butyl-3-carboxynonyltetrahydrophthalic anhydride, while the β -isomer gives the 6-hexenyl-3-carboxyheptyl derivative. *Licanic* and β -eleostearic glycerides³¹ and sorbic esters³² also react with dienophiles.

Diphenyl polyenes add maleic anhydride in the expected manner. 1,6-Diphenyl-1,3,5-hexatriene adds a mole of maleic anhydride in the 1,4-positions;

1,8-diphenyloctatetraene also adds one mole of maleic anhydride in boiling xylene solution at the 1,4-positions. The latter is capable of adding a second mole of maleic anhydride at 5 and 8 positions.³³ 1,10-Diphenyl-1,3,5,7,9-decapentaene is capable of adding two or three moles of maleic anhydride; when only two moles of the anhydride react, addition appears to take place in positions 1,4 and 7, 10.³⁴ In phenyl substituted polyenes, the positions nearest the phenyl groups are the most reactive.

1,3,4,6-Tetrachloro-2,4-hexadiene, 3,6-dichloro-1,3,4-hexadiene, 3,4,6-trichloro-1,2,4-hexatriene, 4-chloro-1,2,3,5-hexatetraene and 3,4-dichloro-1,2,4,5-hexatetraene fail to give adducts with maleic anhydride.

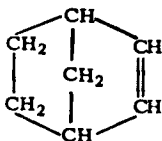
The diene system $\text{—}\overset{\text{I}}{\underset{\text{I}}{\text{C}}}:\overset{\text{I}}{\underset{\text{I}}{\text{C}}}:\overset{\text{I}}{\underset{\text{I}}{\text{C}}}:\overset{\text{I}}{\underset{\text{I}}{\text{C}}}\text{—}$ is capable of adding two molecules of dienophiles, one at the carbon atoms 1 and 4, a second at carbon atoms 3 and 6. Thus, a bicyclic tetrahydrocarboxylic anhydride has been prepared from 2,5-dimethyl-1,5-hexadiene-3-yne and maleic anhydride.

Allenes, i.e., dienes containing the grouping $\text{C}:\text{C}:\text{C}$, do not react with dienophiles. Reaction may occur if the allene undergoes rearrangement to form a conjugated system. Reaction may take place also if at least one of the allene double bonds is conjugated with another double bond. *Cumulenes* also fail to add dienophiles.

Cyclic Dienes

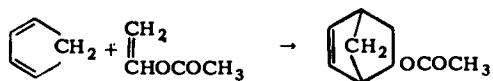
Cyclic dienes generally add dienophiles readily. *Cyclopentadiene* and its derivatives are especially reactive and give excellent yields of adducts, a fact which is probably explained by the fixed character of the system of atoms bearing the conjugated bonds in these compounds.³⁵ Cyclic dienes with five-membered rings react more readily than cyclohexadiene or cyclic dienes with a greater number of carbon atoms in the ring, undoubtedly because the five-membered ring is the least apt to undergo distortion. Alkyl- and aryl-substituted cyclopentadienes appear to react with dienophiles with an ease comparable with that of the parent substance.³⁶ *Cyclopentadienecarboxylic acid* also undergoes reaction with ease.³⁷ *Hexachlorocyclopentadiene* gives adducts with maleic anhydride, acrylonitrile, methyl vinyl ketone, and benzoquinone.³⁸

Cyclopentadiene is capable of reacting even with ethylene and propylene.³⁹ The yield of adduct with the former is quite low, but reaction with propylene gives bicyclo-(2,2,1)-heptene in good yield. Reaction with haloethylenes gives halonorbornylene, vinyl chloride giving dehydronorbornyl chloride which can be reduced to norbornylene chloride, and this can be converted to norbornylene

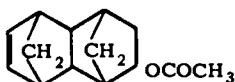


by cleavage of hydrogen chloride.

The diene reacts smoothly with vinyl acetate, giving, in the presence of an excess of the latter, the acetate of a bicyclic alcohol:

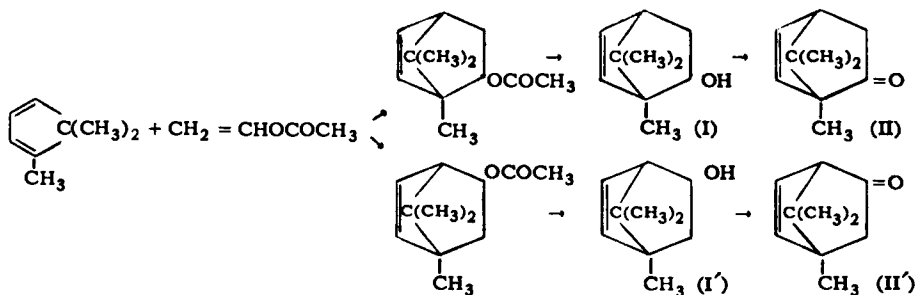


The compound



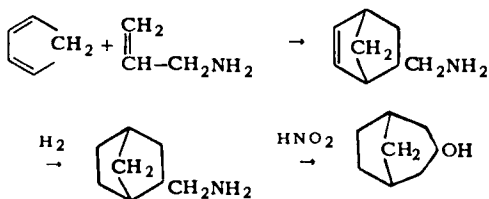
is formed as a by-product in the reaction. This compound may be obtained as the main product when a larger proportion of the diene is employed, and the reaction is carried out at a higher temperature. Oxidation of the alcohol obtained by the hydrolysis of the bicyclic acetate results in the formation of dehydrocamphor, which, on reduction, gives norcamphor. The reduction of the latter, by the Wolff-Kisher method, gives norbornylene.⁴⁰

The reaction of 1,5,5-trimethyl-1,3-cyclopentadiene with vinyl acetate results in the formation of two isomeric adducts, one of which may be converted by steps to borneol (I) and camphor (II), the other to epiborneol (I') and epicamphor (II').⁴¹

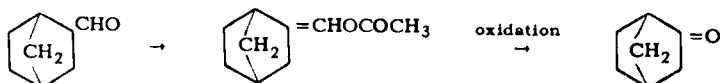


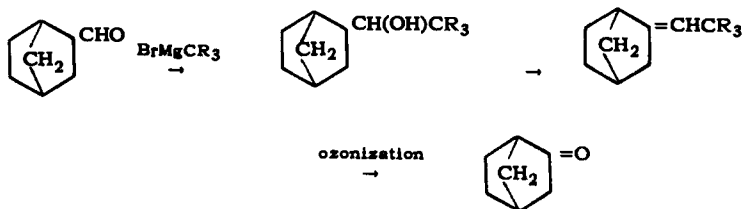
On reduction by the Wolff-Kishner method both camphor and epicamphor yield camphane.

Allylamine gives an adduct with cyclopentadiene which, when hydrogenated and treated with nitrous acid, yields an alcohol of the bicyclo-(3,2)-octane series, the reaction involving a ring enlargement:⁴²

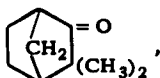


The adduct of *acrolein* with cyclopentadiene has been reduced to the fully saturated aldehyde, which has served as the starting point for the preparation of norcamphor by the two alternative routes shown below:⁴³



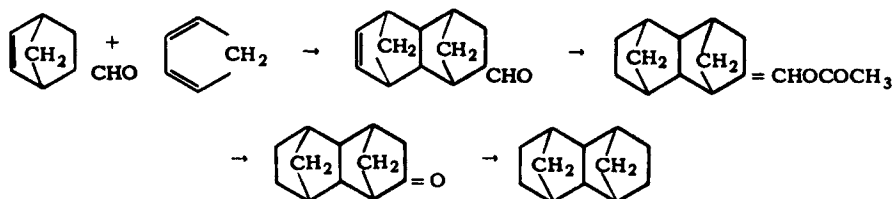


Camphenilone,

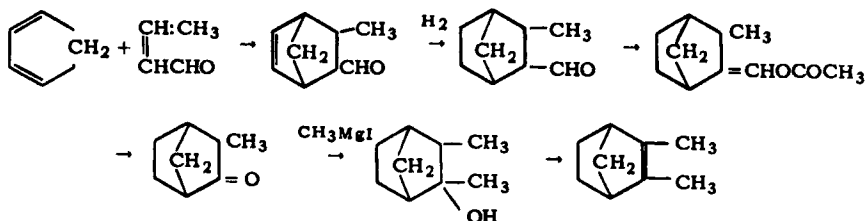


has been synthesized from norcamphor by repeated treatment with sodium amide and methyl iodide.

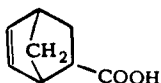
The compound obtained by the addition of a second molecule of cyclopentadiene to the adduct of this diene with acrolein has been converted to 1,4,5,8-bis(endomethylene)decalin by hydrogenation to the saturated aldehyde, formation of the enol acetate of this, oxidation of the latter to a cyclic ketone, and finally reduction of this to the hydrocarbon:⁴⁴



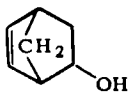
The adduct of cyclopentadiene with *crotonaldehyde* has been converted to santene by the following steps: hydrogenation to the saturated aldehyde, conversion of this to the enol acetate, oxidation of the latter to a cyclic ketone followed by reaction with methylmagnesium iodide, and finally dehydration of the alcohol obtained by the hydrolysis of the halomagnesium complex, dehydration being accomplished by heating with potassium sulfate:⁴⁰



The adduct of *acrylic acid* with cyclopentadiene,

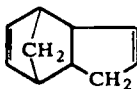


has been converted to norborneol,

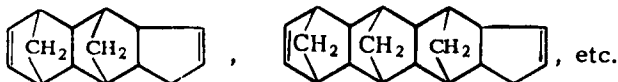


by the following series of transformations: conversion of the acid to its chloride and of this to the acid azide, conversion of the azide into norbornylamine by means of the Curtius degradation, and finally treatment of the amine with nitrous acid.⁴⁵

Cyclopentadiene, in common with other cyclic and acyclic amines, readily undergoes dimerization by a diene condensation giving



This dimer dissociates when heated to between 100 and 150°. It is also capable, however, of further condensation with the monomeric diene, giving successively

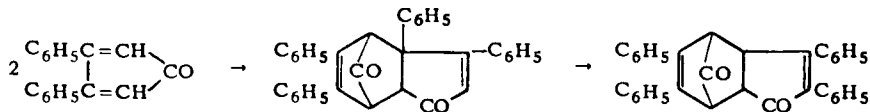


These higher polymers are more heat stable than the dimer; for this reason reactions with cyclopentadiene, when carried out at excessive temperatures, may give low yields due to the formation of higher polymers.⁴⁶

Cyclopentadiene gives an adduct with dicyanoacetylene.

Cyclopentadienone is not known, while its simpler derivatives are known only in the dimeric form, although the transitory existence of the monomers has been demonstrated.

The oxime of cyclopentadienone is known, and it has been established that the compound exists in the monomeric form. A number of other cyclopentadienone derivatives are known to exist in the monomeric form, among these are tetrachloro-, 2,3,4- and 2,3,5-triphenyl, 2-methyl-3,4-diphenyl-, and 2,5-dimethyl-3,4-diphenylcyclopentadienones. Cyclopentadienone derivatives with phenyl groups at 1 and 4 positions of the butadienoid system, i.e., 2,5-diphenyl substituted butadienes, do not dimerize even under extreme conditions. Dimerization of 3,4-diphenylcyclopentadienone proceeds with a shift in the position of one phenyl group:



Cyclopentadienone derivatives are prepared through the dehydration of anhydroacetonebenzils. The monomeric diene is invariably formed first in this reaction. Dimerization, if it should occur, takes place rapidly. It is possible, however, to cause dienophiles to react with the monomer of the diene at the moment it is formed.⁴⁷

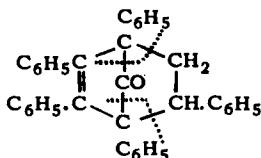
The more complex derivatives of cyclopentadienone are reactive dienes and combine even with dienophiles of low reactivity such as acetylene, butadiene and acenaphthylene.

The adduct of cyclopentadienone derivatives with dienophiles loses the *endo* carbonyl group when heated. This cleavage may be traced to the effect of unsaturated linkages in the molecule.

According to the *double bond rule*, in an unsaturated system such as



the strength of the bond between carbon atoms 3 and 4 is less than that between carbon atoms 2 and 3, so that should cleavage of the chain occur, it will be the result of the rupture of the former bond.⁴⁸ It will be expected that in an adduct of cyclopentadienone derivative such as



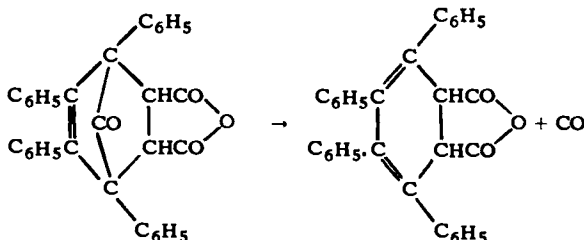
cleavage may cause the liberation of either the carbonyl group or the original dienophile. These cleavages probably occur simultaneously, but while the dienophile will recombine with the liberated diene to regenerate the adduct, cleavage of the carbonyl group is an irreversible process. It follows, therefore that long continued heating will result in a more or less complete removal of the endocarbonyl group. Decarbonylation generally proceeds in the temperature range 200–220°, although with some adducts it proceeds at an appreciable rate at 75–80°.

All adducts of cyclopentadienone derivatives examined have phenyl groups attached to the unsaturated carbon atom. It has been impossible to reduce the double bond in such compounds, so that saturated carbonyl bridge compounds of this type are not known.

In adducts of cyclopentadienone with acetylenic dienophiles, the bonds joining the carbonyl group to the carbon atoms at the bridgeheads are under the weakening influence of two unsaturated groups. Such adducts, therefore, lose carbon monoxide more readily. The instability of the carbonyl bridge is so pronounced in effect that cleavage of the CO group takes place spontaneously in the course of the reaction, and it has been impossible or difficult to isolate the original adducts. The adduct of phenylcyclopentadienone with phenylpropionic acid forms an exception due, it would appear, to the formation of an internal lactone involving the carbonyl group.⁴⁹

Diene syntheses with cyclopentadienone derivatives have been confined almost exclusively to phenyl derivatives and derivatives with fused benzene rings.

Tetraphenylcyclopentadienone, otherwise known as *tetracyclone* has been condensed with a variety of dienophiles.⁵⁰ The adduct with maleic anhydride, when decarbonylated, yields tetraphenyldihydrophthalic anhydride:⁵¹



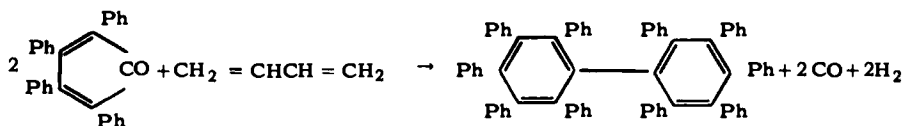
This compound forms an adduct with a second molecule of maleic anhydride; when the resulting compound is heated with barium hydroxide, it yields tetraphenyl benzene.⁵²

The method is applicable to other derivatives of cyclopentadienone and may serve for the preparation of highly substituted benzene derivatives.⁵³

If the condensation of tetracyclone with maleic anhydride is carried out in boiling nitrobenzene, the adduct is dehydrogenated and tetraphenylphthalic anhydride results. Tetraphenylphthalic anhydride has also been prepared from tetracyclone and chlor-maleic anhydride, the adduct losing carbon monoxide and hydrogen chloride under the conditions of the reaction.⁵⁴

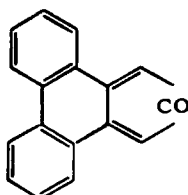
Other unsaturated dibasic acids and their esters have also been condensed with tetracyclone.

An adduct of two molecular proportions of tetracyclone with one of butadiene has been prepared; decarboxylation and aromatization of the resulting adduct gave octaphenylbiphenyl:⁵⁵



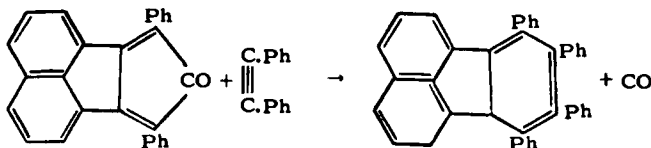
Adducts of tetraphenylcyclopentadienone with acetylenic compounds are unstable and lose carbon monoxide readily to give fully aromatic compounds. Thus, pentaphenylbenzoic acid is obtained with phenylpropionic acid, and hexaphenylbenzene with diphenylacetylene. Reaction with phenylpropionic diethyl acetal results in the formation of pentaphenylbenzaldehyde diethyl acetal, from which the corresponding aldehyde may be obtained by hydrolysis with an acid.⁵⁶

Phencyclone,



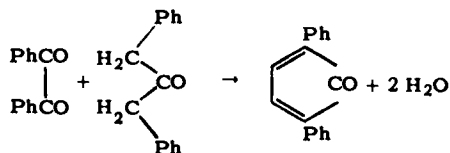
gives adducts with *p*-benzoquinone, naphthoquinone, and naphthazarin diacetate.⁵⁷ The carbonyl bridge in these adducts may be removed by heating, and the resulting quinone may be reduced to the corresponding polynuclear hydrocarbon. This method thus offers a means for the preparation of diphenyldibenzanthracenes, diphenylnaphthacenes and related hydrocarbons.

Acencyclone and tolane react to give a tetraphenylated hydrocarbon:⁵⁷



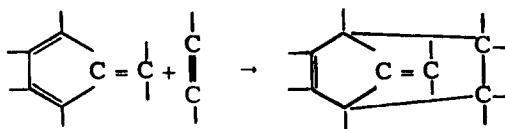
Less reactive dienophiles, such as acetylene, butadiene, and cyclohexene also give adducts with acencyclone.

The general method of preparation of arylated cyclopentadienones is illustrated by the preparation of tetraphenylcyclopentadienone. This compound is obtained through the condensation of dibenzyl ketone with benzil:⁵⁸



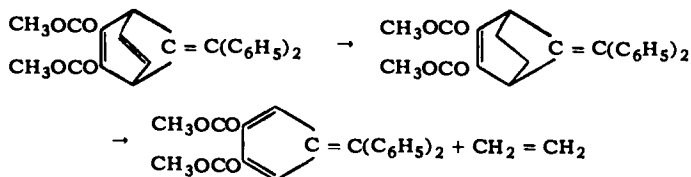
The method is of general application. Other diketones, such as phenanthraquinone, acenaphthoquinone and aceanthraquinone may be used in place of benzil.⁵⁹

Fulvene derivatives give adducts with dienophiles, with the conjugated bonds in the ring alone involved in the reaction:



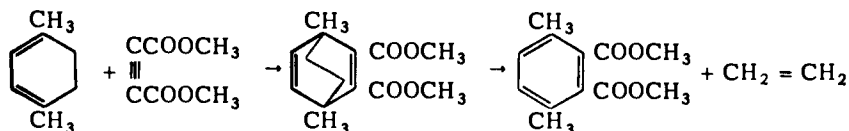
The reaction proceeds with ease in every case, even in dilute solution at room temperature. The adducts with maleic anhydride are readily dissociated, although they are stabilized on reduction of the remaining double bond in the ring.

The adduct of diphenylfulvene and methyl acetylenedicarboxylate, partially hydrogenated and heated, decomposes smoothly to ethylene and methyl diphenylfulvenedicarboxylate:



1,3-Cyclohexadiene and its derivatives add many dienophiles, the reaction proceeding normally in almost all cases, and leading to the formation of compounds of the bicyclooctane series. The reaction proceeds less readily, as a rule, than with the corresponding cyclopentadienes, although quantitative yields of the adducts may be obtained with cyclohexadiene and many dienophiles even when the reaction is carried out in dilute solution and at room temperature. Moderate heating may be required in some instances, but temperatures in excess of 160° should be avoided in order to prevent the dimerization of the diene.⁶⁰

The bicyclooctadiene system in adducts of cyclohexadiene is unstable, and decomposes on heating into ethylene or an ethylene homolog and a dihydrobenzene or benzene derivative. Cleavage of the ethylene group takes place most readily with acetylenic adducts:⁶¹

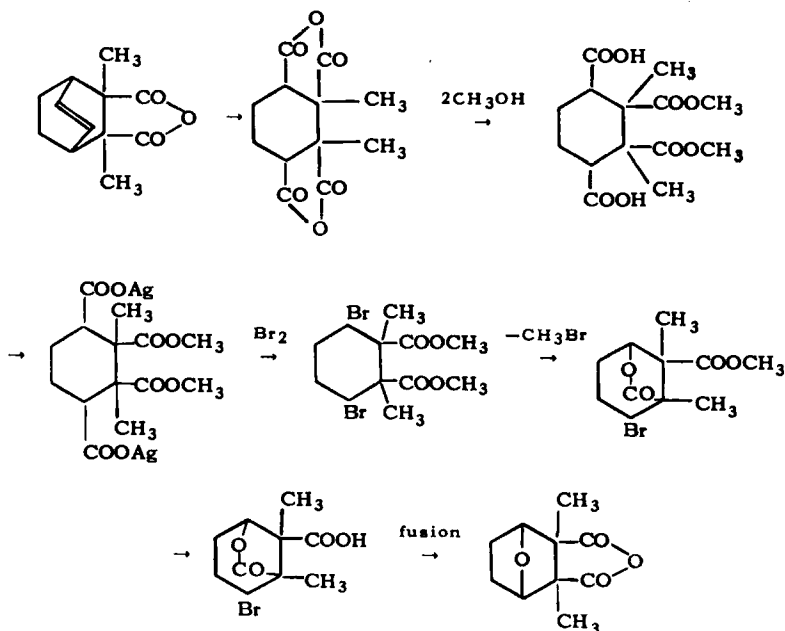


Decomposition with acetylenic adducts proceeds on distillation of the compound.

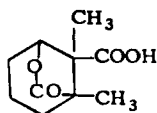
The reaction of cyclohexadiene with maleic acid and maleic anhydride proceeds very readily, a quantitative yield of the adduct being obtained when the components are allowed to react at room temperature in benzene solution.⁶² The diene also reacts readily with quinone, reaction proceeding with quantitative yield in alcoholic solution at room temperature. Di-(cyclohexadiene)-quinone may be obtained with an excess of the diene when the reaction is carried out at 100°. Maleic anhydride also reacts with ease with isopropyl-2,4-cyclohexadiene, dihydro-*o*-tolualdehyde and 1,2-dihydronaphthalic anhydride.⁶³

Cyclohexadiene and acrolein combine at 100° to form 2,5-endomethylene- Δ^3 -tetrahydrobenzaldehyde. The semicarbazone of this aldehyde has been reduced to the semicarbazone of the corresponding saturated aldehyde. The free aldehyde converted to the enol acetate by treatment with acetic anhydride and sodium acetate, then subjected to the action of ozone, gives 2,5-endoethylenecyclohexanone in low yield.⁶⁴

The adduct of cyclohexadiene with pyrocinchonic anhydride is of interest in that it can be used as the starting point for the synthesis of *cantharidin*. The steps involved in this synthesis are, oxidation to a tetracarboxylic acid anhydride, partial esterification of this with methanol, treatment of the silver salt of the acid ester with bromine, and fusion of the resulting brominated lactone:⁶⁵



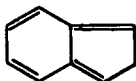
Cantharidin is obtained as the minor product from the fusion of the acid lactone, the principal product being



1,3-Cycloheptadiene derivatives add dienophiles, reaction apparently pro-

ceeding in a normal manner.⁶⁶ The propano bridge in the adducts is thermally stable. *Eucarvone*, which is a cycloheptadiene derivative, is capable of adding maleic anhydride.⁶⁷

Indene reacts as a diene toward such compounds as maleic anhydride and ethyl acetylene dicarboxylate,⁶⁸ the tautomeric form of the compound, benzo-cyclopentadiene,

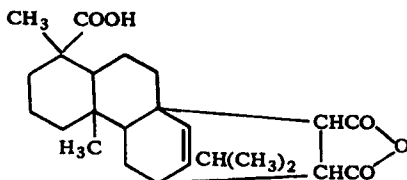


entering into reaction with these dienophiles at higher temperatures. Under relatively drastic conditions, reaction with two molecular equivalents of maleic anhydride takes place, forming endo-*cis*-3,4-benzo-3,6-endomethylene-1,2,3,6-tetrahydrophthalic anhydride.

Many *terpens hydrocarbons* having a conjugated diene system, such as α -phellandrene⁶⁹ and α -terpinene⁷⁰ and others,⁷¹ add maleic anhydride with great ease. β -Phellandrene gives amorphous products with maleic anhydride.

The adduct of maleic anhydride with α -terpinene has attained commercial importance. Its esters with simple alcohols appear to possess insecticidal power. The properties of resins derived from the adduct anhydride may be modified by the introduction of substituents such as CH_3 , $\text{CH}(\text{CH}_3)_2$ or $-\text{CH}_2\text{CH}_2-$ groups. Condensation may be carried out also with certain terpenes lacking conjugated double bonds.

Levopimaric and *abietic acids* among the three principal resin acids possess conjugated double bonds. The first mentioned reacts readily with maleic anhydride with evolution of heat, while reaction with abietic acid proceeds only on heating for several hours at $150-160^\circ$. The adducts formed with the two acids are identical.⁷² Abietic acid apparently undergoes isomerization and is converted to levopimaric acid prior to reaction. The adduct is assumed to possess the structure

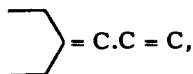


Heated with selenium at 300° it is converted to retene.

Ergosterol and other *sterols* with a similar distribution of double bonds in ring B add maleic anhydride under forced conditions.⁷³ The reaction is best carried out by heating the acetyl derivative of the sterol with the anhydride in benzene or xylene solution at 135° for 8 hours. The adducts undergo dissociation into their components when heated. This decomposition is of preparative value and may be carried out suitably under high vacuum. Maleic anhydride distills first, then follows the sterol or its acetyl derivative.

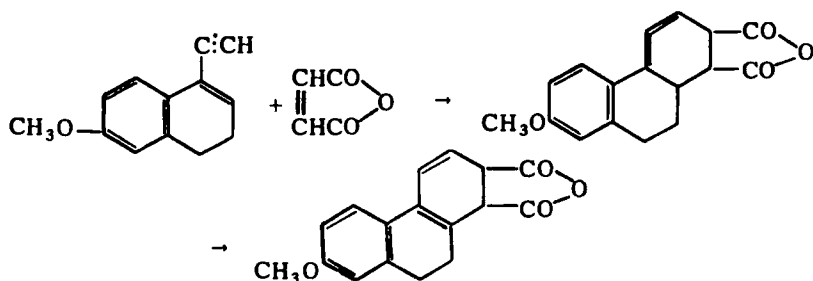
Dehydroergosterol, which contains a system of conjugated double bonds distributed in rings B and C, reacts with maleic anhydride at room temperature. A quantitative yield of the adduct may be obtained by heating the components in benzene solution for four hours.⁷⁴ Addition apparently takes place solely at the double bonds in ring B, since on stereochemical grounds, a 1,4-addition cannot take place in a condensed ring system in which the double bonds are distributed between two contiguous rings.

Conjugated dienes in which one double bond is in an open chain, while the other is a semi-cyclic double bond,

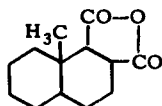


are incapable of reacting with dienophiles. Conjugated dienes in which one double bond is semi-cyclic while the other is in a ring also fail to react.

Dienes in which the conjugated double bond system is distributed between a ring and a side chain are capable of condensing with dienophiles, forming compounds with two fused rings.⁷⁵ This reaction is of considerable preparative value, since many dienes of the type in question are accessible; they are obtained through the condensation of certain acetylenic compounds with cyclic ketones. A typical example of the application of the method is the preparation of 7-methoxytetrahydrophenanthrene-1,2-dianhydride from 6-methoxy-3,4-dihydronaphthyl-1-acetylene and maleic anhydride:⁷⁶



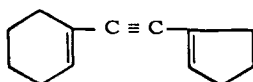
Adducts obtained with 1-vinyl-2-methyl-1-cyclohexene are notable in that they contain an "angular" methyl group, as is observed, for example, in the maleic anhydride adduct,



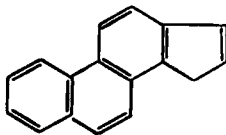
Benzologs of these dienes have been the subject of numerous investigations. Such compounds are of special interest, since some among them, such as 6-methoxy-1-vinyl-3,4-dihydronaphthalene, give adducts related in their structure to the sterols.⁷⁷

The diene condensation of 1-vinylcyclohexene with p-benzoquinone results in the formation of compounds with three or five fused six-membered rings, depending on the proportion of components and the reaction conditions.⁷⁸

A hydrocyclopentenone derivative results through the condensation of two molecules of maleic anhydride with 1-cyclohexenyl-1-cyclopentenylacetylene,

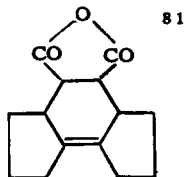


dehydrogenation and decarboxylation of which yields cyclopentanophenanthrene.⁷⁹



Contrary to the rule postulated by Bredt⁸⁰ that addition of a dienophile to cyclic dienes can occur only when the two double bonds of the diene system lie in the same ring, many examples are known of diene addition in which the conjugated system of double bonds is distributed between two neighboring rings. The essential condition required in order that the diene reaction can occur, is that the two double bonds of the conjugated system be in *cis* position relatively to one another; or they must be capable of undergoing rearrangement to this position under the conditions of the reaction. A conjugated diene system consisting of double bonds present in two adjacent rings of a fused ring system obviously cannot satisfy this condition.

Bis-1,1'-cyclopentenyl adds maleic anhydride to form the dicarboxylic anhydride



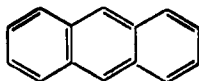
Similarly, *1,1'-octahydrobiphenyl*, reacting with dienophiles, gives derivatives of the phenanthrene series.⁸² The behavior of benzologs of such dienes has been investigated and it has been found that *bis-1-indenyl* and *1,1'-bidialin* give anhydrides similar to those obtained with *bis-cyclopentenyl* and *bis-cyclohexenyl*.⁷⁸

Bicyclic dienes of the type of *bis-1,1'-cyclohexenyl* are formed through the partial reduction of cyclic ketones. Pinacol-like diols are obtained as the intermediate product which are dehydrated to the bicyclic diene. Numerous dienes of the general form-

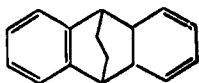
ula $\text{CH}_2(\text{CH}_2)_n\text{CH} = \text{C} \cdot \text{C} = \text{CH}(\text{CH}_2)_n\text{CH}_2$ and their derivatives have been prepared by this method.

Aromatic Dienes

Simple aromatic compounds of the benzene, naphthalene, biphenyl, phenanthrene, chrysene and pyrene series do not give adducts with dienophiles. Addition takes place when the molecule contains a system of at least three *linearly* fused rings such as is present in anthracene



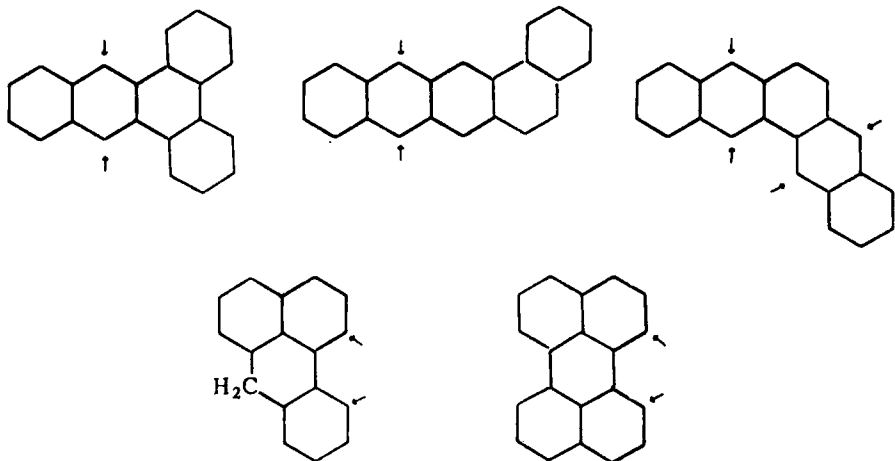
This compound and its derivatives exhibit good diene activity, the dienophile adding, without exception, to the conjugated system of the *central* nucleus⁸³ and giving derivatives of bicyclo-(2,2,2)-octane



It should be noted that it is not possible to assign complete Kekulé structures to all rings of anthracene, and other polynuclear compounds capable of adding dienophiles.

The velocity of adduct formation with derivatives of anthracene varies according to the character of substituents at the 9, 10 positions, if such are present.⁸⁴ Substituents in other positions exert only a slight influence. Phenyl groups and halogens at the 9, 10 positions decrease the reactivity, while methyl groups cause its increase; other alkyl groups exert little effect. Among the simpler derivatives of anthracene, 9-bromo-, 9-nitro-, 9-carbethoxy-anthracene, bis-9-anthrylamine and 9-bromoanthracene-10-carboxylic acid are capable of yielding adducts with maleic anhydride.⁸⁵

The addition of a fused benzene ring at 1,2-position causes a decrease in the diene activity of anthracene, while addition at 2,3-position brings about an increase in reactivity. The addition of two such fused rings, one at 2,3-position, and one at 6,7-position enhances diene activity to such a degree that the compound reacts instantaneously with maleic anhydride.⁸⁶ The points of attack with some polynuclear aromatic hydrocarbons showing diene activity are indicated below by arrows:



More highly condensed systems containing the perylene skeleton add dienophiles in the same manner as perylene.⁸⁷

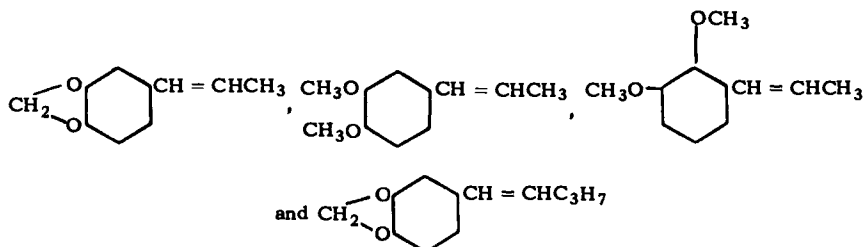
2,3,10,11-Dibenzo-, 1,2,6'-oxido-1,2-benzo-, 3,9-dichloro-, 3,9-dibenzoyl- and 1,2-diphenylaceperylene give adducts with maleic anhydride, while 1,12-benzo-, 3,4,9,10-tetrachloro-, 3,4,9,10-tetranitroperylene and periflanthene fail to react.⁸⁸

The adducts of polycyclic aromatic compounds are readily dissociated into their components on heating; for this reason, it is often important to use an excess of the dienophile and to employ a solvent of low boiling point in order to secure a good yield. The unfavorable effect of higher temperatures on the yield may be appreciated by the

fact that equimolecular quantities of methylcholanthrene and maleic anhydride give a 94% yield of the adduct in boiling benzene, and only 22% yield in boiling xylene.

Aromatic-acyclic compounds, such as *styrene*, in which a double bond in the side chain is conjugated with one in the ring, act as dienophile components, although usually under forced conditions. A 1,4-addition takes place, involving the double bond in the side chain and a Kekulé bond in the adjacent benzene ring, a new double bond making its appearance between the linking carbon atoms of the ring and side chain.

Styrene itself does not yield a monomeric adduct with maleic anhydride, although *anethole*, i.e., 1-(*p*-methoxyphenyl)-1-propene, apparently reacts in a normal manner.⁸⁹ As a general rule, styrene derivatives with an alkyl substituent in the β -position in the side chain, and an alkoxy group in the aromatic ring in *meta* position with respect to the side chain react normally with maleic anhydride, forming a monomeric adduct. A second condition must also be satisfied, however, namely, that the carbon atom at which ring fusion will occur should be in the *para* position with respect to the alkoxy group.⁹⁰ Thus, the compounds



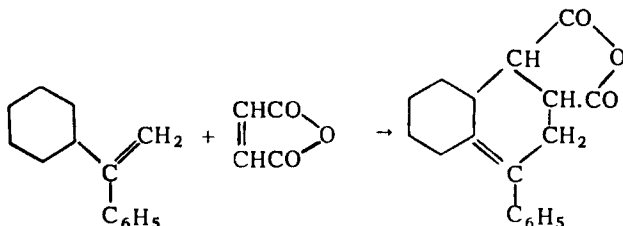
all form adducts with maleic anhydride, ethyl maleate, ethyl acetylenedicarboxylate and chlormaleic anhydride. Isoeugenol and isosafrole also form adducts with diethyl maleate.

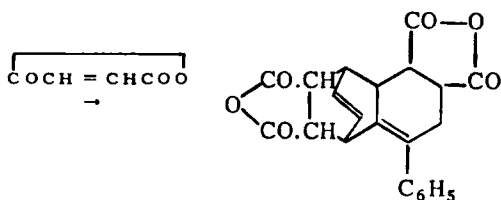
An alkoxy group in the *para* position with respect to the side chain enhances the ability of the styrene derivatives to combine with maleic anhydride, while one at the *meta* position does not exert such an effect.⁹¹

The adduct of β -bromostyrene with maleic anhydride is readily dehydrobrominated on heating to naphthalene-1,2-dicarboxylic anhydride. The latter is obtained, in the form of its methyl ester, through the condensation of 1,2-dihydronaphthalene with methyl acetylenedicarboxylate.

Adducts of styrene show a tendency toward aromatization through an intramolecular migration of hydrogen, and spontaneous dehydrogenation, the dienophile acting as the hydrogen acceptor.⁹²

The condensation of maleic anhydride with *asym-diphenylethylene* leads to the formation of a bis adduct:⁹³



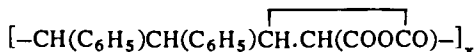


This adduct may be converted to 1-phenyl-1,2,3,4-tetrahydronaphthalene by treatment with hydrogen iodide in acetic acid solution, and this product may be fully aromatized to phenylnaphthalene by distilling with zinc dust. This series of transformations, leading to the formation of a substituted naphthalene, has come to be known as the *Wagner-Jauregg reaction*. It is applicable to other unsymmetrical diaryl ethylenes. When the two aromatic groups are different, the ring with the greater "resonance" contribution participates exclusively in the addition to the dienophile.⁹⁴

Adducts obtained from diarylvinyl bromides lose a molecule of maleic anhydride, one of hydrogen bromide and hydrogen, when sublimed in vacuum, and are thus fully aromatized to derivatives of naphthalene-1,2-dicarboxylic anhydride.⁹⁵

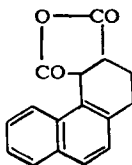
Diarylethylenes containing β -naphthyl or 9-phenanthryl groups give low yields of adducts the structure of which remains to be established.⁹⁶

Stilbene, $C_6H_5CH=CHC_6H_5$, reacts with maleic anhydride in boiling benzene to form a high molecular adduct. The reaction proceeds by a so-called additive heteropolymerization. The formula



has been proposed for the compound.

α -Vinyl*naphthalene* is capable of adding dienophiles to form monomeric adducts, the reaction taking place more readily than with styrene.⁹⁷ β -Vinyl*naphthalene* also adds dienophiles, the reaction with maleic anhydride resulting in the formation of 2,3,4-tetrahydrophenanthrene-3, 4-dicarboxylic anhydride.⁹⁸



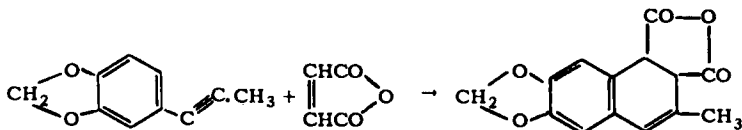
9-Vinyl*phenanthrene* adds dienophiles forming partially hydrogenated derivatives of tri-*o*-phenylene.

As a general rule, 1,2,3-triarylbutadienes fail to react with dienophiles, while 1,1,2- and 1,2,4-isomers are capable of reaction.⁹⁹

β -Isopropenylanthracene adds a molecule of maleic anhydride.¹⁰⁰

Asym-diphenylethylene is capable of reacting with acetylenedicarboxylic acid methyl ester to form an adduct which on hydrolysis and dehydrogenation gives 1-phenylnaph-

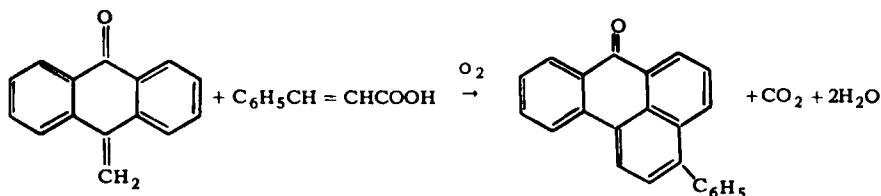
thalene-3,4-naphthalenedicarboxylic acid.⁹³ An acetylenic group attached to a phenyl group, and therefore conjugated with an aromatic double bond, also may be capable of reacting with dienophiles. Thus, methylene-3,4-dioxyphenylmethylacetylene forms an adduct with maleic anhydride:



The semi-cyclic double bond in 9-methyleneanthrone and its derivatives acts as part of an active conjugated diene system, and these compounds react with ease with many dienophiles, giving derivatives of benzanthrone or analogous higher condensation products of the anthracene series.¹⁰¹ The initial adduct contains a conjugated diene system in a cyclohexadiene ring, and is capable of adding another molecule of diene. With maleic anhydride, successive addition of two molecules of the anhydride takes place.

The adducts are partially hydrogenated derivatives, and may be readily dehydrogenated to their parent hydrocarbons with hot nitrobenzene. Dehydrogenation takes place automatically when this compound is used as a solvent in the preparation of the adduct.

The reaction of cinnamic acid with methylanthrone in boiling nitrobenzene results in the formation of Bz-1-phenylbenzanthrone, decarboxylation and oxidation occurring simultaneously:



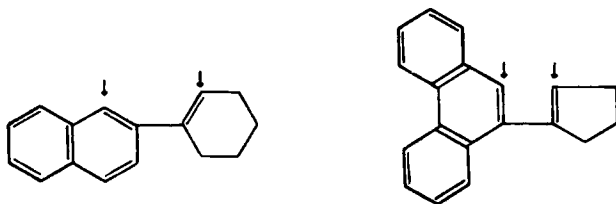
A similar decarboxylation occurs in the reaction with fumaric acid, the product being benzanthrone Bz-1-carboxylic acid. Benzoyl ethylene gives a Bz-1-benzoylphenanthrene, while stilbene yields a diphenylbenzanthrone.¹⁰²

When an excess of methyleneanthrone reacts with *p*-benzoquinone, an adduct is obtained which is oxidized by atmospheric oxygen to bis-(benzanthrone-Bz-1,2)-2,3,5,6-benzoquinone.¹⁰³

ω -Phenylene-methyleneanthrone and ω -(2-anthraquinoyl)-methyleneanthrone are capable of adding dienophiles.¹⁰⁴

Aromatic-acyclic dienes in which a semi-cyclic double bond is conjugated with a double bond in the acyclic portion of the molecule, such as is observed in vinylbenzofulvene, do not give adducts with dienophiles.¹⁰⁵

Aromatic-alicyclic compounds in which a double bond in the alicyclic ring is conjugated with a double bond in the aromatic ring are capable of adding dienes. Thus, β -(1-cyclohexenyl)-naphthalene and 10-(1-cyclopentenyl)-phenanthrene add dienophiles. The points of attack are indicated in the formulas given below by arrows:



A partially dehydrogenated sterol derivative has been obtained from β -(1-cyclopentenyl)-naphthalene by reaction with maleic anhydride.¹⁰⁶

Partially *hydrogenated phenanthrene* derivatives which have a pair of conjugated double bonds react normally with dienophiles. Even highly substituted compounds of this type are capable of reacting with dienophiles; thus, *thebaine* gives adducts with maleic anhydride and with quinone.¹⁰⁷

Indene reacts with maleic anhydride under relatively drastic conditions to form endo-*cis*-3,4-benzo-3,6-endomethylene-1,2,3-tetrahydrophthalic anhydride.

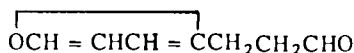
The following compounds fail to give adducts with maleic anhydride: 1- α -naphthyl-1-cyclohexene, α -9-phenanthrylstilbene, 9-(1-cyclohexenyl)-phenanthrene, 1-(9-phenanthryl)-1-phenylethylene and 9,9'-biphenanthryl.¹⁰⁸

Anthrones fail to undergo the normal 1,4-diene addition, but react in the *ketonic* form with anhydrides of the type of maleic anhydride to give anthronyl-succinic anhydrides.¹⁰⁹

Heterocyclic Dienes

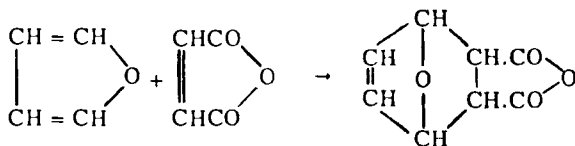
Heterocyclic dienes differ widely in their reactivity toward dienophiles. Some, like furans and coumalins, are capable of giving the normal adducts, while others, including thiophene and pyrrole, fail to give 1,4-adducts.

Heterocyclic compounds with an oxygen atom in the ring generally undergo the normal diene reaction, although a tendency toward substitution is also shown by these compounds. In effect, 1,4-addition of dienophiles in furan and methyl furan is prevented if sulfur dioxide and other sulfur containing compounds are present, and a substitution type reaction takes place instead,¹¹⁰ acrolein giving with furan, for example, the compound



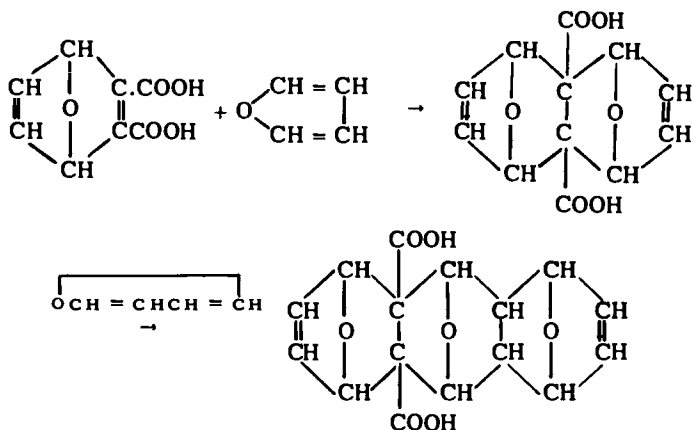
in low yield.

Adducts obtained with furan and its derivatives contain an oxygen bridge:



Multiple addition has been observed with the adduct of furan and acetylenedi-

carboxylic ester, additional molecules of furan combining with the adduct, addition first taking place at the unsaturated atoms bearing the carboxyl group:¹¹¹



Only the most active dienophiles, such as maleic anhydride and acetylene dicarboxylic esters, react with the simple furans. Pyrocinchonic anhydride, tetrolic ester and sym-dimethylmaleic anhydride fail to react with the simpler furans.¹¹² Many of the more complex furans are capable of reaction with a wide range of dienophiles.

The adducts of furan and its derivatives are unstable and undergo dissociation in solution, the degree of dissociation depending, in some measure, upon the character of the substituents in the furan molecule. In some instances dissociation takes place at room temperature, even the isolated pure solids undergoing spontaneous decomposition in some cases.¹¹³ Dissociation is often complete when the adduct is heated above its melting point, especially if the furan component is volatile. Because of the unstable character of the adduct, the reaction should not be carried out at temperatures in excess of 100-120°. This is not a serious limitation, however, since the reaction often proceeds rapidly at room temperature, and a quantitative yield of the adduct may be obtained if a solvent is employed which does not retain in solution the adduct formed.

Because of the instability of adducts of furan and its derivatives, it has been considered possible that they are loose molecular compounds. The fact, however, that reduction^(*) of the remaining double bond in the furan ring in the adduct results in the complete stabilization of the compounds demonstrates that normal adduct formation has taken place.

The oxygen bridge in furan adducts is not generally removable by heat, and is stable in other respects.¹¹⁴ When partially hydrogenated adducts are heated, cleavage takes place at the ethylenic bridge, the partially hydrogenated adduct of sylvan and acetylenedicarboxylic ester, for example, giving 2-methyl-3,4-furandicarboxylic ester.¹¹⁵ De-

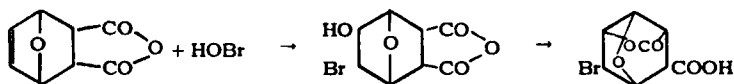
(*) Hydrogenated furan adducts generally have a vesicant action on the skin.¹¹²

composition proceeds smoothly on heating the hydrogenated adduct and the method is of preparative value.

The oxygen bridge in these adducts is sensitive, however, toward acids, and removal of the oxygen often takes place with great ease upon treatment with hydrogen halides, with resultant aromatization of the ring system. Dihalo compounds are apparently formed as intermediates, upon treatment of the adducts with hydrogen halides, and may be isolated as such if no substituents are present in the adduct at the bridge carbon atoms. If substituents are present at the bridge carbon atom, dehydrohalogenation takes place automatically at room temperature, and results in the formation of an aromatized system. Dihalo compounds that have been isolated have proven to be very unstable, and subject to dehydrohalogenation on slight heating.

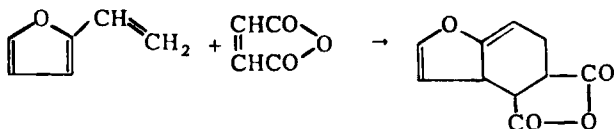
The oxygen bridge in the hydrogenated adduct may also be removed readily by treatment with hydrogen halides. The partially hydrogenated adducts with acetylenedicarboxylic acid give benzene derivatives by this treatment.

The adduct of furan and maleic anhydride adds hypobromous acid at the double bond, and the resulting bromo hydroxy compound lactonizes readily:



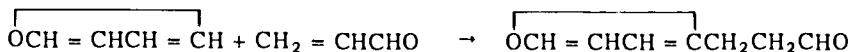
The adduct of acetylene dicarboxylic ester with two moles of maleic anhydride also reacts in a similar manner, combining with two molecular equivalents of hypobromous acid, and eventually undergoes a double lactonization.¹¹¹

Many furan derivatives are capable of adding dienophiles; thus, normal adduct formation has been observed, among others, with α - and β -methylfuran, α, α' -dimethylfuran, α - and β -bromofuran, β -hydroxyfuran, furfuryl methyl ether, furfuryl acetate, furfural diacetate, furfuryl acetone and α -furyl- γ -phenylpropane.¹¹⁷ α -Vinylfuran shows an exceptional behavior, and adds maleic anhydride in the following manner:¹¹⁸

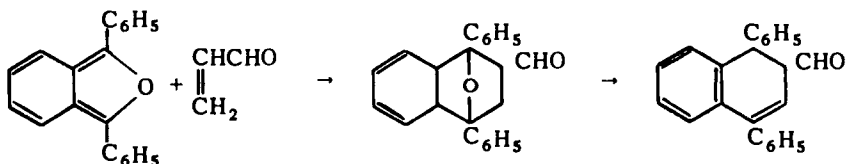


No adducts have been obtained with furans with a carbethoxy, cyano or nitro group directly attached to the ring¹¹⁹ and with α -hydroxyfuran.¹²⁰

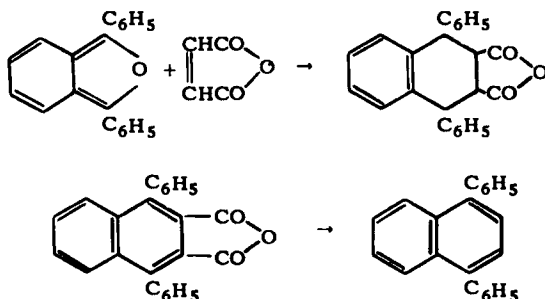
Traces of sulfuric acid or sulfur dioxide, sulfonic acids or their chlorides promote the so-called substitution reaction, exemplified by the formation of β -(2-furyl)-propionaldehyde from furan and acrolein:



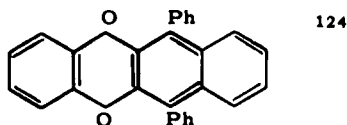
The fusion of the furan system with a six-membered ring, such as is observed in the *isobenzofuran* type of compounds, does not diminish the additive power of the furan double bonds.¹²¹ Thus, the reaction of α, α' -diphenyl- β, β' -benzo-furan and acrolein leads to the formation of an adduct which, on elimination of the oxygen bridge, yields 1,4-diphenylnaphthalene-2-aldehyde.¹²²



The adduct of α,α -diphenyl- β,β' -benzofuran with maleic anhydride, aromatized and subsequently decarboxylated, gives 1,4-diphenylnaphthalene:¹²³

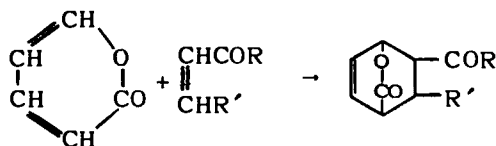


The condensation of the same diene with 1,4-naphthoquinone gives an adduct which, on treatment with hydrochloric or sulfuric acid, yields

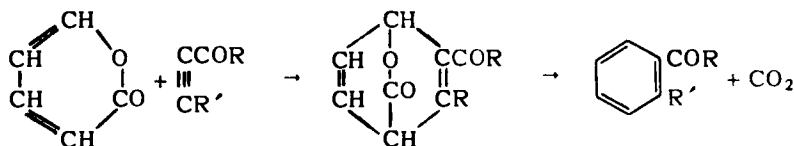


1,3-Bis(α -naphthyl)-isobenzofuran forms adducts with maleic anhydride and acrolein,¹²⁵ and 1,3-bis-(3,5-dibromo-4-hydroxyphenyl)-isobenzofuran with maleic anhydride or ester, the reaction with the latter furan compound taking place in boiling toluene.¹²⁶ 1,3-Diphenyl-5,6-dimethylbenzofuran also adds maleic anhydride, but the reaction is so readily reversible that purification of the adduct is difficult.¹²⁷

Coumalins, which are lactones containing conjugated double bonds, give adducts containing a lactone bridge:¹²⁸



These compounds lose a molecule of carbon dioxide on heating. Adducts formed with acetylenic compounds give fully aromatic products after decarboxylation:



Dissociation takes place readily in a high boiling solvent and proceeds smoothly with maleic anhydride adducts when an excess of this anhydride is employed.

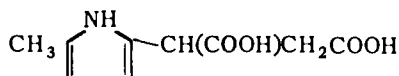
γ -Pyrones do not form adducts with dienophiles. Many of the simple cyclic α,β -unsaturated ketones also fail to form adducts with dienophiles, or form adducts with difficulty.¹²⁹

Thiophene, like benzene, does not add dienophiles;¹³⁰ tetraphenylthiophene also fails to undergo the diene addition. Thiotolenes and thioxenes probably also are incapable of reacting with dienophiles. 1,3-Diphenylisobenzothiophene fails to react with maleic anhydride,¹³¹ but 1,3,5,6-tetraphenylisobenzothiophene¹³² and 2,3,4,5-bis-(1,8-naphthalene)-thiophene¹³³ give adducts with the anhydride, the latter yielding 3,4,5,6-bis-(1,8-naphthalene)-phthalic anhydride by loss of hydrogen sulfide.

Pyrrole does not form normal adducts with dienophiles, but gives addition compounds according to the scheme:

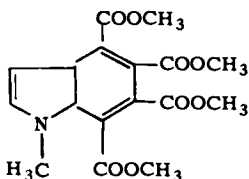


7-Methylpyrrole, for example, reacting with maleic anhydride in aqueous solution, gives 2-methyl-5-pyrrolylsuccinic acid,¹³⁴



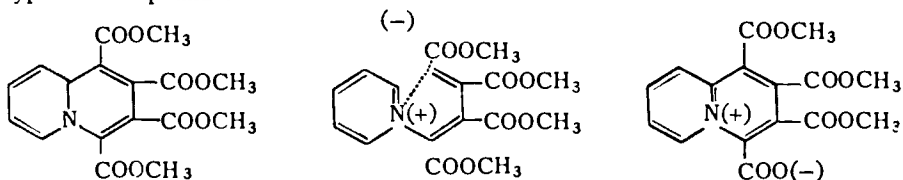
while 1-methylpyrrole gives 1-methyl-2,5-pyrroledisuccinic acid.

1-Methylpyrrole reacts with acetylenedicarboxylic ester to form the adduct

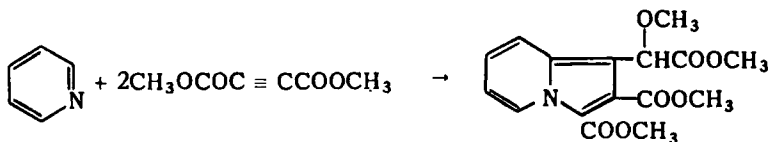


This compound may be aromatized by treatment with bromine, and subsequently saponified and decarboxylated to N-methylindole in good yield.¹³⁵

Normal diene addition fails to take place also with *pyridine* and its *homologs*. These compounds are capable of reacting with acetylenedicarboxylic ester to form condensed ring systems with nitrogen as one of the bridge atoms.¹³⁶ The reaction with pyridine in ethereal solution results in the formation of three types of compounds:



In methyl alcoholic solution, the reaction proceeds otherwise, a fused ring system with five- and six-membered rings resulting:¹³⁷



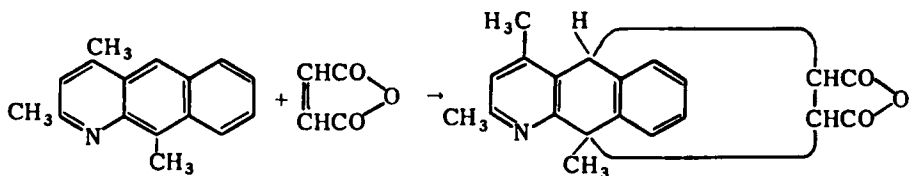
The glycolic ether residue in this compound may be replaced with the nitro group by treatment with a mixture of nitric and acetic acid, and the resulting nitro compound may be reduced to an amino compound.

α -Picoline¹³⁸ and quinoline¹³⁹ react with acetylenedicarboxylic ester in ethereal solution in a manner similar to pyridine. The quinoline adduct is readily oxidized by chromic acid or dilute nitric acid to an indolizin derivative. Similar adducts are obtained with isoquinoline.¹⁴⁰ 9-Phenanthridine reacts in a similar manner.¹⁴¹ The reaction of acridine with acetylene dicarboxylic ester gives a variety of products.¹⁴²

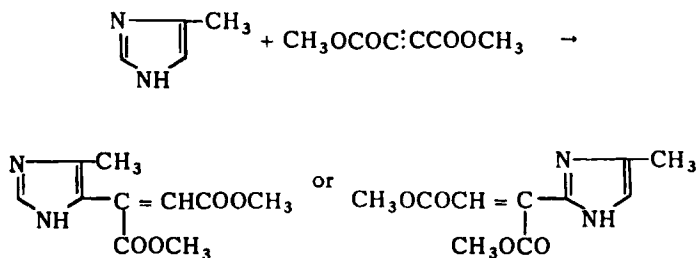
2-Styrylquinoline does not form an adduct with maleic anhydride, but gives 2-styrylquinolinium maleate.

Derivatives of α -dihydropyridine, which contain a pair of conjugated double bonds in a six-membered ring, act as reactive dienes.¹⁴³ If the dihydropyridine carries a hydrogen atom joined to nitrogen, dehydrogenation occurs, the dienophile acting as the hydrogen acceptor.¹⁴⁴

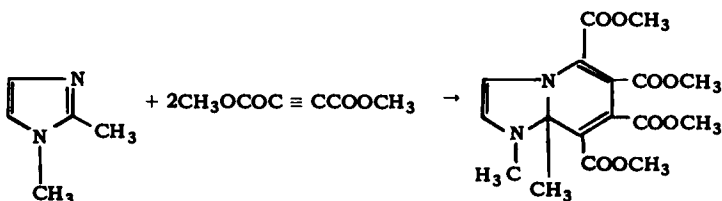
The addition of maleic anhydride to the *meso* positions of anthracene is not generally paralleled in heterocyclic compounds of similar structure,¹⁴⁵ although 2,4,10-trimethylbenzo(g)-quinoline gives a normal adduct with maleic anhydride:¹⁴⁶



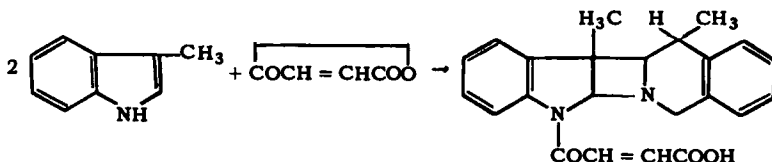
The reaction of imidazoles with acetylenedicarboxylic acid is similar to that of pyrroles:



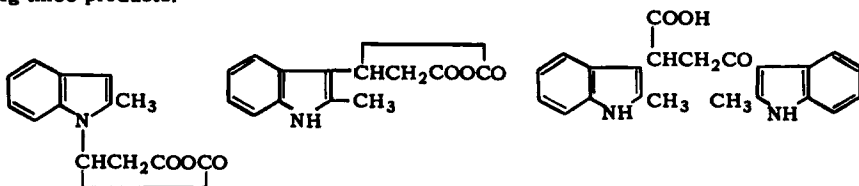
1,2-Dimethylimidazole reacts with two molecules of acetylenedicarboxylic ester in a manner resembling the reaction of pyridine with the acetylenic ester:



Indoles react in an abnormal and generally complex manner with maleic anhydride, acetylenedicarboxylic esters, and *p*-benzoquinone.¹⁴⁷ Thus, the reaction of maleic anhydride with skatole involves dimerization of the latter and an amide formation with the anhydride:

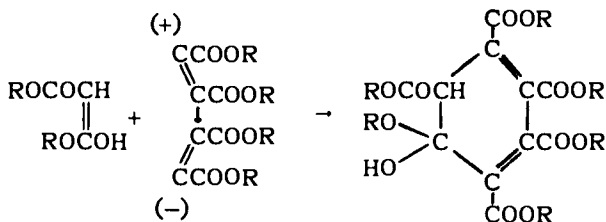


Indole reacts in a similar manner, but α -methylindole reacts in an unusual manner, giving three products:



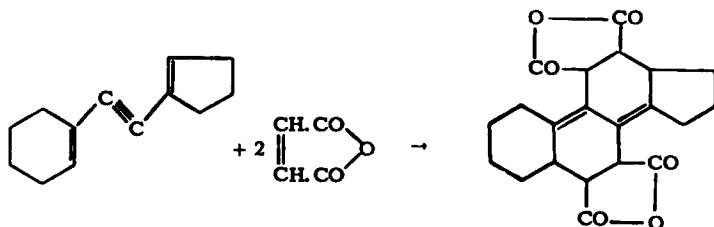
Enynes

A system consisting of a triple bond conjugated with a double bond, present in the so-called enynes, may add dienophiles to form a normal 1,4-adduct. In the process of addition, the enyne apparently first changes to the tautomeric zwitterion, which adds to the dienophile.¹⁴⁸ This tendency toward zwitterion formation is observed in the reaction of acetylene dicarboxylic ester with pyridine and other similar bases,¹⁴⁹ and in the reaction of this ester with malonic esters in the presence of pyridine, the malonates reacting in the enolic form:¹³⁰



The formation of 1,3,5-triphenylbenzene from phenylacetylene apparently also takes place by a similar mechanism.¹⁵¹ The dimerization of 3-methyl-3-pentene-1-yne is a further example of this type of addition.

A clear cut case of normal adduct formation involving the acetylenic bond is offered by the reaction of 1-cyclohexenyl-1-cyclopentenylacetylene, which adds two molecules of maleic anhydride:¹⁵²



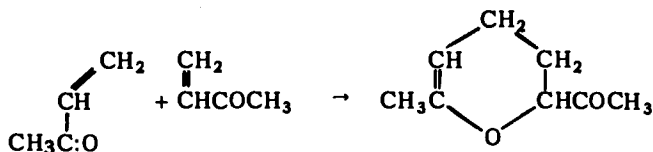
The yield of adducts with enynes are generally low.

6,9-Dimethyltetradeca-5,9-dien-7-yne and 4,7-di-n-propyldeca-3,7-dien-5-yne have been condensed with two molecular proportions of maleic anhydride. The products appear to be amorphous.¹⁵³

Dienes with Other than Carbon-to-Carbon Double Bonds

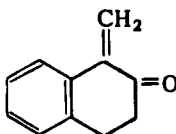
The diene addition may involve conjugated double bonds between carbon atoms and atoms of elements other than carbon. Thus, the systems $O:C:C:O$, and $N \equiv C:C \equiv N$ may undergo the diene condensation, although the scope of applicability of the synthesis to such systems is very narrow.

The dimerization of vinyl ketones is an example of diene reaction with the group $C = C:C = O$.



The reaction, which generally takes place with great ease, always proceeds in such a manner that the carbonyl group in the adduct is in the closest proximity to the oxygen of the pyran ring. Vinyl ethyl ketone, vinyl methyl ketone,

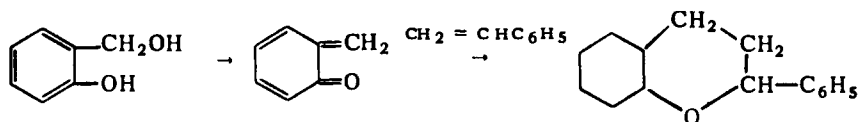
acrolein, o-methylenecyclohexanone, $CH_2(CH_2)_3C(=CH_2)CO$, and naphthoquinone-(1,2)-methide,



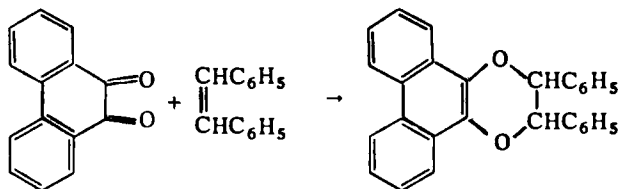
undergo such a dimerization.¹⁵⁴ The two last named compounds dimerize rapidly at the moment of their formation.

The reaction readily proceeds further to give high polymers by a chain mechanism, although this can generally be prevented by the use of inhibitors.

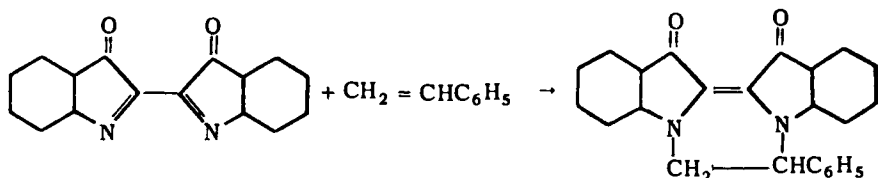
o-Hydroxybenzyl alcohol gives adducts with various dienophiles. There is little doubt that dehydration of this compound to *o*-methylenequinone precedes adduct formation:¹⁵⁵



The group $-\text{CO.CO}-$ present in phenanthraquinone undergoes a diene type addition, under the action of sunlight, with ethylene derivatives such as styrene, stilbene and triphenylethylene:¹⁵⁶



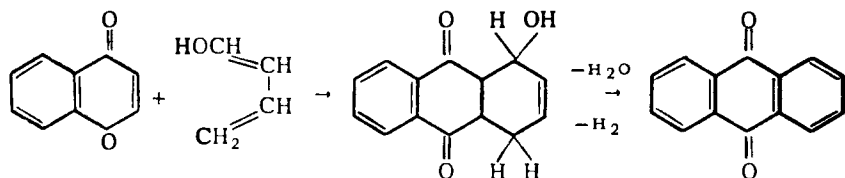
The system $\text{N}=\text{C.C}=\text{N}$ present in dehydroindigo is capable of adding styrene to form styreneindigo:



Other dienes are also capable of forming adducts of a similar type with dehydroindigo.¹⁵⁷ It is a remarkable fact, however, that dienophiles such as maleic anhydride and quinone, which are generally very reactive toward dienes, fail to react with dehydroindigo.

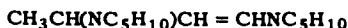
ψ -Dienes

Certain compounds normally devoid of a conjugated diene system may, under the conditions of the diene synthesis, react as dienes. A typical example is presented by crotonaldehyde, $\text{CH}_3\text{CH}=\text{CHCHO}$, which reacts in the tautomeric diene form in the presence of piperidine, giving with α -naphthoquinone an adduct, which, after dehydration and aromatization, is converted to anthraquinone:¹⁵⁸



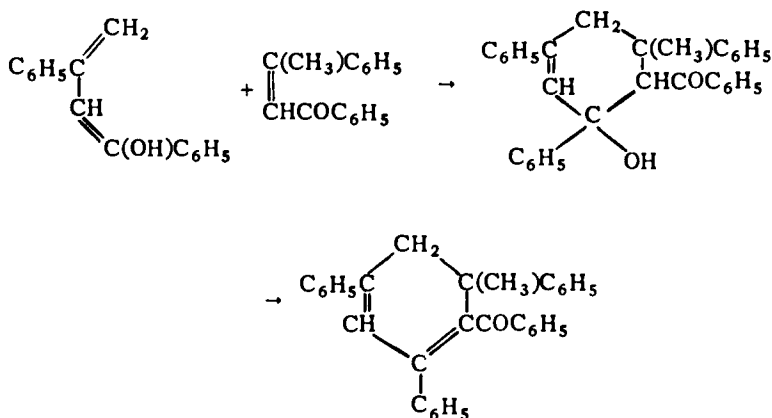
o-Chloro and methyl-crotonaldehyde also react as typical ψ -dienes. Other α,β -unsaturated carbonyl compounds undergo enolization of the same type under the influence of proton-loosening agents such as sodamide, sodium alcoholate, etc.¹⁵⁹

It may be noted that crotonaldehyde and piperidine combine in ethereal solution in the presence of potassium carbonate to form 1,3-bis-piperidinobutene-1,

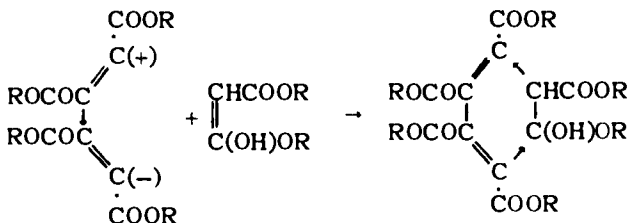


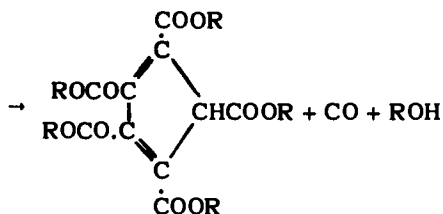
and that, when this compound is heated in the presence of catalytic quantities of high molecular carboxylic acids or quinones, it is converted to 1-piperidinobutene-1,3, $\text{CH}_2=\text{CHCH}=\text{CHNC}_5\text{H}_{10}$.¹⁶⁰ The ready tautomerization of crotonaldehyde is also indicated by the formation of 1-acetoxybutadiene, $\text{CH}_2=\text{CHCH}=\text{CHOCOC}_2\text{H}_5$, at boiling temperature, from crotonaldehyde and acetic anhydride in the presence of sodium acetate.¹⁶¹

The reaction of benzalacetophenone with dypnone in the presence of sodium ethoxide is of similar type, dypnone reacting in the tautomeric diene form, $\text{C}_6\text{H}_5\text{C}(\text{OH})=\text{CHC}(\text{C}_6\text{H}_5)=\text{CH}_2$.¹⁶² Dypnopinacone formation also involves the reaction of the enolic form of dypnone with the normal form:¹⁶³

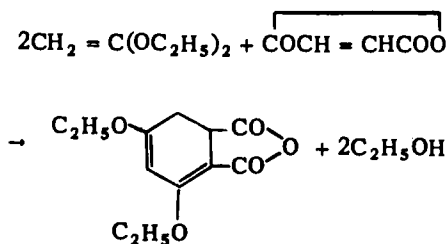


The ester of malonic acid may also react in the enolic form as a diene component, a diene addition with two molecular equivalents of acetylenedicarboxylic acid giving the ester of pentadienepentacarboxylic acid:



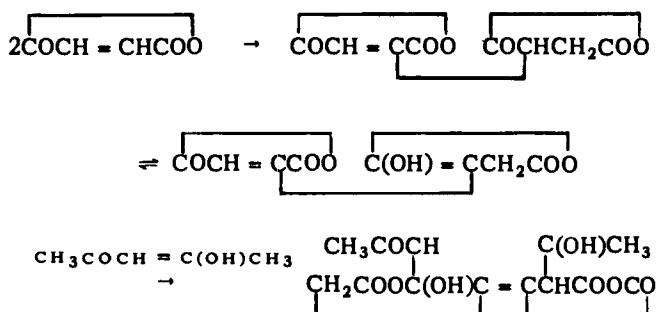


Ketene acetal reacts in an unusual manner with maleic anhydride; two molecules of the acetal react with one of anhydride to form a cyclic addition product, which changes to diethoxydihydrophthalic anhydride with loss of two molecules of ethanol:¹⁶⁴

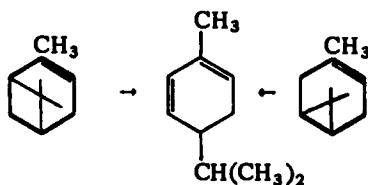


Dimethylmaleic anhydride does not react with ketene diacetal, while acetylenedicarboxylic ester reacts in the same manner as maleic anhydride, giving 3,5-diethoxyphthalic ester.

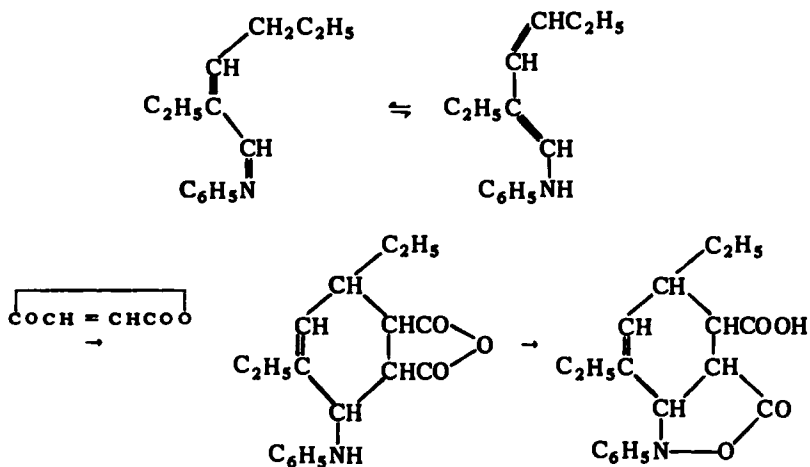
The condensation of acetylacetone with maleic anhydride apparently involves the previous formation of a diene by the union of two molecules of maleic anhydride:¹⁶⁵



Another group of ψ -dienes is represented by compounds in which a double bond and a labile ring are present; rupture of the ring in these compounds is followed by the appearance of a double bond conjugated with that originally present in the compound. α -Pinene and β -carene are examples of such compounds, both giving the same diene:

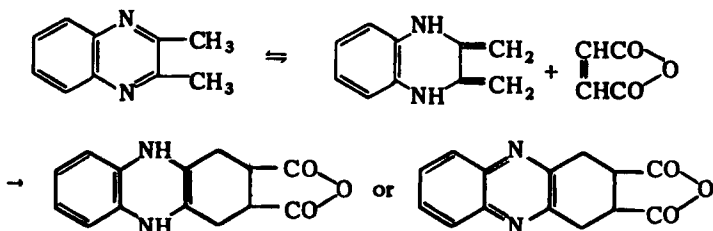


When 2-ethyl-2-hexenal-aniline is made to react with maleic anhydride, migration of the double bonds takes place and a normal 1,4-diene addition then follows:¹⁶⁶



Cinnamalaniline fails to undergo a similar reaction because the initial tautomerization cannot occur.¹⁶⁷

3,4-Dimethylquinoxaline reacts in the tautomeric form with maleic anhydride forming a hexahydrophenazinedicarboxylic anhydride:¹⁶⁸



DIENOPHILE COMPONENTS

As has been pointed out, the ability of the simpler olefinic hydrocarbons to form adducts with dienes is not marked. The reactivity of the unsaturated bond toward dienes is increased by certain groups joined to the unsaturated carbon atoms. Among activating groups, the carbonyl, and carboxyl groups produce a

marked increase in activity, two such groups attached to the two unsaturated carbon atoms causing a greater increase in activity than a single group. Other groups causing activation of the ethylenic bond are CN, NO₂, and SO₂R. Some activation is also caused by CH₂COOH, CH₂Cl, CH₂OH, CH₂NH₂, CH₂NCS, OCOR, Cl, Br, OR and SR. Unsaturated groups and aromatic residues also cause activation of the double bond. If two activating groups are present these may be attached to the same carbon atom, or to each of the unsaturated carbon atoms. The more reactive dienophiles, it may be noted, are compounds the double bonds in which add ammonia, amines and hydrogen cyanide with ease.

The dienophile group may be present in a ring. One double bond in certain cyclic dienes is capable of acting as a dienophile to combine with a second molecule of the diene to form a dimer. The active dienophile group may be present in a fused ring system. Quinones as a class, with some exceptions, are highly active dienophiles.

Many acetylenic compounds act as dienophiles. Acetylenedicarboxylic acid and its esters are especially reactive dienophiles. Groups which cause the activation of ethylenic bonds also cause the activation of acetylenic bonds.

Acyclic Dienophiles

α,β-Unsaturated carbonyl compounds usually are reactive dienophiles; acrolein, methyl vinyl ketone and phenyl vinyl ketone are representative of this group of dienophiles. The reaction of *cis*- and *trans*-dibenzoylthylenes with the appropriate dienes has served for the preparation of 1,3-diarylisobenzofurans, *o*-diarylbenzenes and their hydrogenated derivatives.¹⁶⁹ Some compounds of this type fail to react with the less reactive dienes.¹⁷⁰ Methyl vinyl ketone and phenyl vinyl ketone, for example, fail to react with furan; phenyl vinyl ketone fails to condense with cyclohexadiene. Benzalacetophenone and dibenzylethylene do not give adducts with tetraphenylcyclopentadienone. The terminal methyl groups in *β,β*-dimethylacrolein appear to cause retardation of the reaction of the compound with dienes.

Ketenes are capable of adding dienes, but the process of addition differs from the normal diene reaction in that it is a 1,2-addition. The adducts, therefore, contain a four membered ring. Thus, diphenylketene and cyclopentadiene react at room temperature to form a dicyclic ketone with a four and a five membered ring:¹⁷¹

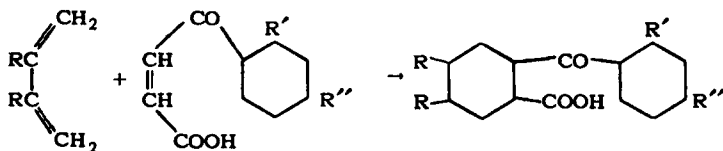


α,β-Unsaturated acids such as acrylic, crotonic, sorbic, cinnamic and substituted cinnamic acids are active dienophiles. Acids which in the free state are unstable at the temperature at which the reaction is carried out, such as ethylidenemalononic and ethoxymethyleneacetoacetic acids are employed in the form of their esters. *Maleic acid*, its homologs and derivatives are reactive

dienophiles, although with the more highly substituted derivatives it may be necessary to carry out the reaction at higher temperatures. Methylene malonic acid, $\text{CH}_2 = \text{C}(\text{COOH})_2$, and methyleneacetoacetic acid, $\text{CH}_2 = \text{C}(\text{COOH})\text{COCH}_3$, are reactive dienes. *o*-Methoxycinnamic acids and the corresponding hydroxy acids react readily with 2,3-dimethylbutadiene, but they react with difficulty with isoprene and do not react with butadiene. Esters of ethylenetetracarboxylic acid, and of substituted methylenemalonic acids, $\text{RCH} = \text{C}(\text{COOH})_2$, add dienes with great ease, giving alicyclic malonic esters. As a general rule, the yield of adducts from the free acid is more satisfactory than from the esters.

Derivatives of hydrobiphenyl have been obtained through the reaction of butadiene with cinnamic acids, and have been used extensively in the synthesis of dibenzopyrones and their hydrogenated derivatives, hydrofluorenones and hydrophenanthridines.¹⁶⁹ Hexahydrofluorenones have been prepared from the condensation products of cinnamic and substituted cinnamic acids with 2,3-dimethylbutadiene, by cyclization of the chlorides of the acids obtained. Octahydrophenanthridines have been prepared from these by ring enlargement by the hydrazoic acid method followed by replacement of the oxygen with sulfur by use of phosphorus pentasulfide, and finally electrolytic reduction of the thio compound at a lead cathode.

A number of anthraquinone derivatives have been prepared from the adducts of β -aroylacrylic acids and acyclic dienes.¹⁷²



These adducts are obtained in quantitative yield by reaction in alcoholic solution at 100° . While the adducts cannot be directly cyclized, cyclization occurs readily after aromatization with elemental sulfur, anthraquinones resulting in many cases in 40% yield.

Unsaturated *acid chlorides* show a strong tendency to polymerize under the conditions of diene synthesis, and for this reason their use for this purpose is limited. Normal adducts of *trans* crotyl chloride and cyclopentadiene have been obtained, however, by carrying out the reaction at -10° .¹⁷³

A limited number of α,β -unsaturated lactones have been investigated as to their ability to undergo the diene addition; the results indicate that this class of compounds have slight dienophylic reactivity. Adducts have been obtained with butadiene- α,β -butanolide and β -angelica lactone when the reaction was carried out at a temperature in excess of 150° .

Nitro ethylenes show limited reactivity as dienophiles, although many adducts have been obtained successfully with β -nitrostyrene and its 3,4-dimethoxy and 3,4-methylenedioxy derivatives. Nitro ethylenes fail to react under normal conditions with the simple furans, including 3-methyl- and 2,5-dimethylfuran. β -Nitrostyrene has been reported to form adducts, however, with 1,3-diphenylisobenzofuran and its 5,6-dimethyl derivative.

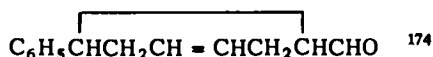
Halogenated ethylenes, such as vinyl chloride, and di- and trichloroethylenes, give adducts with cyclopentadiene. The reactivity of halo ethylenes apparently decreases with increase in the number of halogens in the molecule. Thus, trichloroethylene gives an adduct with cyclopentadiene at a high temperature, while the velocity of adduct formation with tetrachloroethylene is so low that polymerization becomes the main reaction with this compound.

Vinylacetic acid, $\text{CH}_2 = \text{CHCH}_2\text{COOH}$, and its nitrile, allyl halides



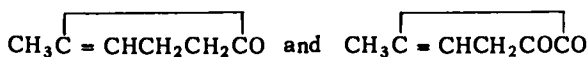
allylamine and allyl alcohol show some reactivity as dienophiles and are capable of adding smoothly to cyclopentadiene at elevated temperatures. The esters of the hypothetical vinyl alcohol, especially vinyl acetate and vinyl formate, also show some reactivity as dienophiles and give adducts with cyclopentadiene, vinyl acetate giving an almost quantitative yield of the adduct when heated at 180° with this compound.

Cinnamaldehyde, $\text{C}_6\text{H}_5\text{CH} = \text{CHCHO}$, functions as a dienophile toward butadiene, combining with this compound at room temperature to give



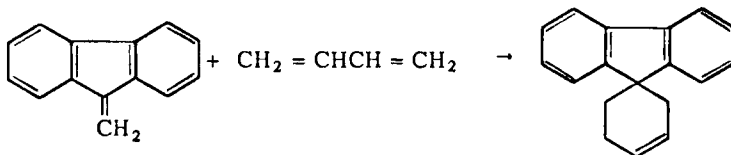
Cyclic Dienophiles

Cyclic unsaturated compounds may act as dienophiles. Cyclohexene and derived hydrocarbons do not undergo the diene synthesis, with bicyclohexenyl, while 1-methylcyclopentene gives an adduct with this diene.¹⁷⁵ The double bond in the adduct of cyclopentadiene and maleic anhydride and other similar adducts is known to act as a dienophile. The double bond in the unsaturated cyclic ketones



also is capable of diene addition. Indene is known to form an adduct with 2,3-dimethylbutadiene.¹⁷⁶

Certain compounds with *semicyclic double bonds* react as dienophiles forming adducts with dienes; the resulting products contain a spirocyclic ring system. The reaction of biphenyleneethylene with butadiene¹⁷⁷ may be cited as an example:

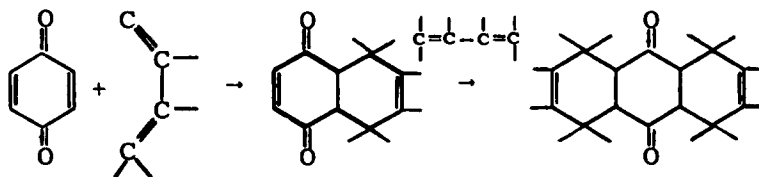


The reaction of dienes with anhydrogossypol apparently involves an addition at a semicyclic double bond.¹²⁰

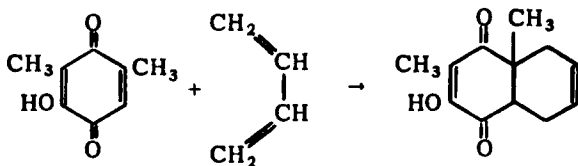
Quinones

Quinones as a class and with few exceptions are among the more reactive cyclic dienophiles, and many are capable of forming adducts even with the less reactive dienes.

p-Benzoquinone is capable of forming adducts with one or two molecular proportions of dienes:



Substituents in the *p*-benzoquinone ring generally exert a retarding action on the reaction with dienes and often completely inhibit the reaction. Carbonyl groups and other groups which activate the ethylenic bonds form an exception. The hindering effect of methyl groups in *p*-xyloquinone is so great that this compound fails to react with dienes in benzene solution at 150°. ¹⁷⁸ Hydrobenzoquinones are capable of forming adducts with dienes, quantitative yields being generally obtained with butadiene on heating the components at 110° in dioxane solution for 20 hours: ¹⁷⁹



Adducts may be obtained similarly with other substituted *p*-benzoquinones, as for example, with thymoquinone and chloranil. ¹⁸⁰

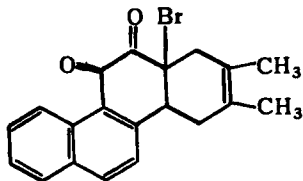
As a general rule, the dienophilic activity of quinones runs parallel with their oxidation-reduction potentials, quinones with a higher potential showing a higher dienophilic activity. ¹⁸¹

The fusion of a fully aromatic ring to the *p*-benzoquinone nucleus completely suppresses the dienophilic activity of the quinoid double bond within the aromatic ring without, however, affecting the reactivity of the other quinonic double bond. Thus, α -naphthoquinone will add but one molecular equivalent of a diene. Substituents in naphthoquinone have the same effect on dienophilic activity as substituents in benzoquinone. ¹⁸² α -Naphthoquinone itself is capable of giving adducts with nearly all compounds with conjugated double bonds that show diene activity. ¹⁸³ The introduction of hydroxyl groups in the benzene ring of α -naphthoquinone results in a decrease in dienophilic activity. ¹⁸⁴

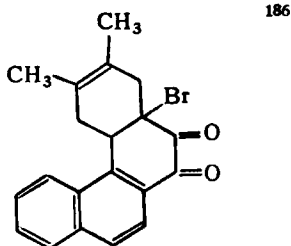
o-Benzoquinone and β -naphthoquinone are unstable toward heat, and when an attempt is made to condense them with dienes, only tarry decomposition prod-

ucts are obtained. A number of substituted β -naphthoquinones are sufficiently heat stable to give adducts with dienes. Adducts are obtained, for example, with 3-substituted β -naphthoquinones, which react more readily than 2-substituted α -naphthoquinones.¹⁸⁵ Reaction with certain dienes proceeds to completion within one hour at 100°. 4-Substituted β -naphthoquinones react less readily than the 3-substituted isomers. A halogen atom in the 3-position exerts a stabilizing effect.¹⁸² As in the case of α -naphthoquinones, the introduction of a hydroxyl group into the benzene ring of β -naphthoquinones decreases the dienophilic activity, and 6- or 7-hydroxy-1,2-naphthoquinones fail to react with 2,3-dimethylbutadiene.¹⁸²

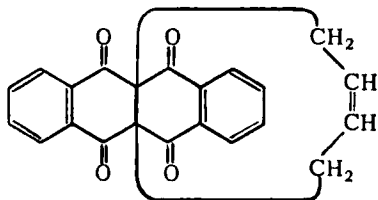
Anthraquinone does not show any dienophilic activity; 9,10-phenanthraquinone is also devoid of dienophilic activity, but 2-bromo-3,4-phenanthraquinone reacts with 2,3-dimethylbutadiene, giving a 90% yield of the adduct



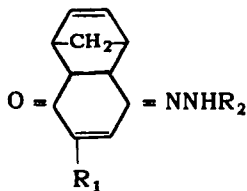
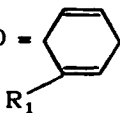
and 3-bromo-1,2-phenanthraquinone reacts with the same diene to give a 58% yield of the adduct



Fusion of two *p*-benzoquinone rings does not destroy the dienophilic activity associated with the unsaturated carbon atoms involved in the fusion.¹⁸⁷ Thus, 9,10,11,12-naphthacenediquinone adds butadiene and 2,3-butadiene readily, giving with the former the adduct



Among nitrogenous analogs of *p*-benzoquinone which add dienes are quinoneazine and various derivatives of 2,4-dinitrobenzeneazo-*p*-phenol. The latter exists partly in the tautomeric form $O = \text{C}_6\text{H}_4 = \text{NNHR}_2$, and give, with cyclopentadiene, compounds of the type:¹⁸⁸



An important property of adducts of quinones with various dienes is the ease with which they are dehydrogenated to the parent aromatic compounds. The transformation may take place on simply subjecting the compound in alkaline medium to the action of atmospheric oxygen. The adduct of α -naphthoquinone with 1,1,3-trimethylbutadiene has been aromatized by this method in alcoholic alkaline solution.¹⁸⁹ The transformation may also be brought about by heating the compound with a mild oxidizing agent, such as nitrobenzene.

Acetylenic Dienophiles

Acetylenic compounds are capable of giving adducts with conjugated dienes by a process of 1,4-addition. Steric effects do not play an important role in the reaction of acetylenic dienophiles with dienes because angular, geminal or spirane groupings are never formed.

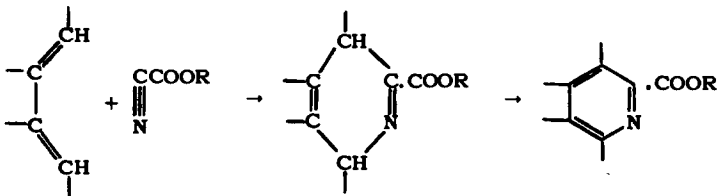
Acetylene itself has been added under forced conditions to highly reactive dienes such as phencyclone. Acetylenic acids such as propiolic acid and acetylenedicarboxylic acid and related compounds show enhanced dienophilic activity, acetylenedicarboxylic acid and its esters showing particularly high reactivity. These compounds react with all types of dienes, although low yields have been reported in the reaction of acetylenedicarboxylic esters with 2,3-diphenylbutadiene and with isosafrole, and methyl acetylenedicarboxylate failed to give an adduct with 9,10-dibromoanthracene.¹⁹⁰ Butynone, $\text{CH} \equiv \text{CCOCH}_3$ and dibenzoylacetylene, $\text{C}_6\text{H}_5\text{COC} \equiv \text{CCOC}_6\text{H}_5$ also react with simple dienes.

Dienophile Systems with Elements other than Carbon

The dienophile character is not confined to unsaturated systems with carbon-to-carbon multiple bonds. Dienophile properties have been observed with compounds with multiple bonds between nitrogen and carbon, nitrogen and oxygen. The types known to have shown dienophilic activity are represented by benzonitrile $\text{N} \equiv \text{CC}_6\text{H}_5$, cyanoformic esters, $\text{N} \equiv \text{CCOOR}$, iminosuccinic esters $\text{ROCOC}(=\text{NR})\text{CH}_2\text{COOR}$, azidocarboxylic acid esters, ROCON:NCOOR , and

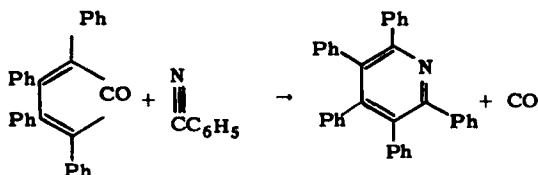
p-nitrosodimethylaniline, $\text{ON.C}_6\text{H}_4\text{N(CH}_3)_2$. The combination of certain unsaturated compounds having conjugated double bonds, with atmospheric oxygen, appears to represent an example of diene addition.¹⁹¹

In the reaction of esters of cyanoformic acid with dienes, a 2,5-dihydropyridine is apparently formed first. If hydrogen is present in the adduct at 2 and 5 positions, dehydrogenation takes place under the reaction conditions, and a pyridine derivative is formed:

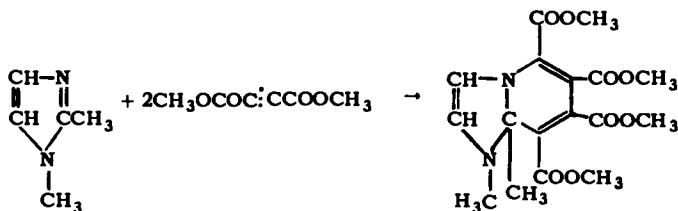


Picolinic acid results, for example, from the reaction of cyanoformic ester with butadiene, and 4,5-dimethylpyridine-2-carboxylic ester results from its reaction with 2,3-dimethylbutadiene.

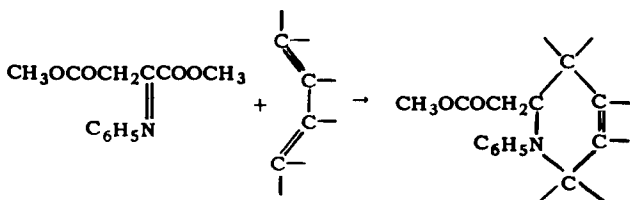
The reaction of benzonitrile with tetraphenylcyclopentadiene, which gives a nitrogen heterocycle with a carbonyl bridge, also leads to the formation of a pyridine derivative upon decarbonylation of the adduct:¹⁹²



1,2-Dimethylglyoxaline reacts with methyl acetylenedicarboxylate in ethereal solution at room temperature to form methyl 1,8-dimethyl-1,8-dihydropyriminazole-4,5,6,7-tetracarboxylate:

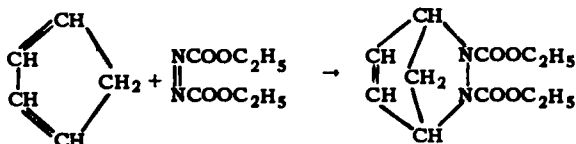


Δ^3 -Piperidine derivatives result through the condensation of dienes with esters of aminomaleic acid acting in the tautomeric iminosuccinic ester form:

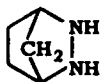


This reaction takes place with aminomaleic esters in which the nitrogen carries a hydrogen atom.

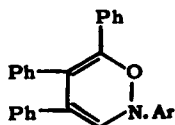
Azodicarboxylic acid esters, ROCON:NCOOR , are highly reactive toward dienes and yield the normal 1,4-adducts,¹⁹³ reaction with cyclopentadiene and the ethyl ester of the azo acid proceeding as follows:



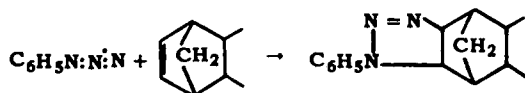
Hydrogenation of the double bond in the adduct followed by saponification of the ester and decarboxylation results in the formation of the alicyclic hydrazo compound



Adducts have been obtained with some aromatic nitroso compounds and tetracyclone and phenacyclone,¹⁹⁴ the $\text{N}=\text{O}$ group acting as the dienophile center. Decarbonylation takes place during the reaction and the intermediate endo carbonyl compound has not been isolated. The product obtained with tetracyclone is



Phenyl azide reacts as a diene toward the double bond in the bicycloheptene ring, forming an adduct with compounds containing such a ring:



The reaction appears to be specific and has been employed as a test for the presence of the bicycloheptene ring in cyclopentadiene polymers.¹⁹⁵

Steric Relations

The steric configuration of adducts resulting from the diene reaction conform to two principal generalizations postulated by Alder.

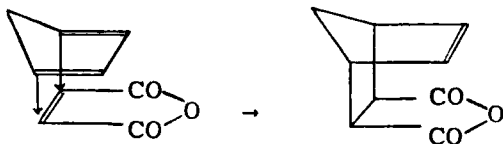
1. The reaction of a dienophile with a diene always proceeds as a *cis* addition, i.e., the new bonds formed as a result of the reaction are in the *cis* position.

The relative positions of substituent groups in the dienophile are retained in the adduct.¹⁹⁶ Thus, maleic acid gives with butadiene *cis*-1,2,3,6-tetrahydrophthalic acid, while fumaric acid gives the *trans* isomer. The *cis* adduct in-

initially formed may undergo isomerization to the *trans* adduct, particularly if the reaction is carried out at an elevated temperature.

2. When a cyclic diene reacts with a cyclic dienophile, addition takes place in such a manner that the planes of the two rings are in close proximity. One may assume that immediately preceding addition, the planes of the reacting rings are so oriented that addition will yield an *endo* structure. The electrostatic forces at work between the reacting molecules possibly play a part in bringing about this orientation.¹⁹⁷

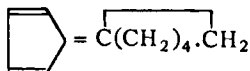
The mode of addition is illustrated by the sketch below, in which the reacting molecules are cyclopentadiene and maleic anhydride:



Alder postulated that in this mode of addition, there is a *maximum accumulation of the unsaturated bonds* just prior to addition, and that this is the real criterion of the steric course of the reaction. In the application of the rule, multiple bonds within the ring as well as external to the ring and those present in substituents are to be taken into account. Thus, in the example shown above, when the double bonds of the carbonyl groups and those in the pentadiene ring are considered, maximum accumulation of double bonds exists when prior to reaction, the molecules are oriented as shown in the sketch to the left.

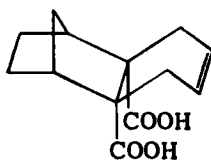
In the reaction of a dienophile with alkylated fulvenes, the application of the rule of maximum accumulation of double bonds does not lead to a definite prediction of orientation, and experience has shown that both *endo* and *exo* additions take place with these compounds. In the case of diphenylfulvene, on the other hand, the rule predicts that addition will take place exclusively in the *exo* direction, and experience has shown that this is indeed the case.

6,6-Pentamethylenefulvene,



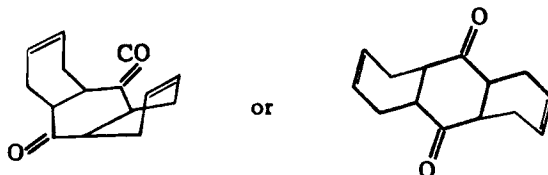
first gives the *endo* adduct with maleic anhydride at room temperature, and on long standing, the *exo* isomer. The formation of the *exo* adduct is favored by high temperatures.¹⁹⁸

The application of the rule to asymmetrically substituted maleic acids shows that the *endo* product should result from the reaction of such dienes with a dienophile. But two distinct modes of addition are possible in such cases. Steric selectivity still holds, and of the two possible isomers from the reaction of 3,6-endomethylene-3,4,5,6-tetrahydrophthalic acid with butadiene, for example, only one isomer, that represented in the following sketch is formed:



Similarly, the dimerization of cyclopentadiene, for example, is an *endo* addition, while further additions are of the *exo* type.

It is known that bis-butadienequinone is formed through exclusive *cis* addition of both molecules of butadiene, giving



more probably the first. These isomers are termed by Alder *cis-cis-ancis-* and *cis-cis-antrans*, respectively.

Fractional Diene Synthesis

Because of differences in the relative ease of addition of a given dienophile to various dienes, it is possible, in certain instances, to eliminate one or more of the dienes from a mixture of several dienes, by adduct formation with a relatively reactive dienophile. This process, which has been designated fractional diene synthesis, has been employed with success for the preparation of pure vitamins D₁, D₂, D₃ and D₄ from the mixture of these vitamins which result when various provitamins are irradiated.¹⁹⁹ Citraconic anhydride is better suited for this purpose than maleic anhydride. The adduct of vitamin D₂ with maleic anhydride is exceptionally stable and may be distilled without decomposition at 250 – 260° under 0.001 mm pressure.

The ready decomposition of the adduct of tachysterol and citraconic anhydride into its components upon distillation under a high vacuum at 165° has been utilized for the isolation of this sterol.²⁰⁰

The principle of fractional diene synthesis has been used also for the isolation and purification of anthracene and other polynuclear hydrocarbons capable of adduct formation with maleic anhydride. As anhydrides of dicarboxylic acids, these adducts react with caustic to form water-soluble alkali metal salts, which may therefore be separated from the unchanged hydrocarbons. The aromatic constituent of the adduct may then be regenerated by heating.²⁰¹

Use of the Diene Addition for the Reversible Blocking of Unsaturated Bonds

The reversible character of the diene reaction makes possible, in those cases in which the adduct is readily dissociated, the use of diene addition as a means of protecting the multiple bonds in the diene or dienophile. Thus, while the reduction of acrylonitrile to allylamine cannot be carried out directly, the

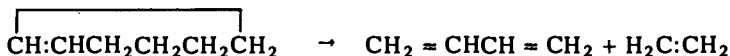
nitrile can be converted to the unsaturated amine by condensing it with anthracene, reducing the nitrile group and finally decomposing the resulting primary amine into allylamine and anthracene by the application of heat.

The direct conversion of acetylenedicarboxylic acid to the chloride is impossible. On the other hand, the carboxylic hydroxyl groups of the adduct of acetylene dicarboxylic acid with anthracene can be replaced with chlorine by the usual methods. The adduct acid chloride forms in 33% yield. The direct thermal dissociation of the adduct chloride cannot be carried out successfully because of the instability of acetylene dicarboxylic chloride. But cleavage of the chloride may be brought about by heating the chloro adduct with maleic anhydride, whereby the latter displaces the acetylenedicarboxylic acid chloride, and forms the maleic anhydride adduct of anthracene.¹¹⁶

An important application of the method is the preparation of certain sterol derivatives. An example is afforded by the preparation of dihydroergosterol (provitamin D₄) from ergosterol. In the latter compound there are two double bonds in conjugated position in ring B, and a double bond between carbon atoms 22 and 23 in the side chain. In all reactions which affect double bonds, all three are attacked simultaneously. When maleic anhydride is made to react with ergosterol, the conjugated bonds in ring B are eliminated, a new double bond making its appearance in ring B. This double bond is of lower reactivity, and it is possible to carry out various reactions, under properly controlled conditions, with the double bond between carbon atoms 22 and 23, without affecting the new double bond. In particular, the double bond in the side chain can be reduced selectively, and on subsequent elimination of maleic anhydride by heating and regeneration of the conjugated system in ring B, dihydroergosterol is obtained.¹⁷⁶ Should reduction be carried out under such vigorous conditions that the double bond in ring B in the adduct is reduced, removal of the maleic anhydride from the resulting compound by heating becomes impossible.

Reverse Diene Synthesis

A number of cases are known of compounds which, when heated strongly, decompose into a diene and an olefinic compound, although the resulting diene and olefin cannot recombine to regenerate the compound. This process has been termed *reverse diene synthesis*. An example is the formation of butadiene and ethylene when cyclohexene is passed over a hot wire:



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PART II

CARBOCYCLIC COMPOUNDS

SECTION 1. ALICYCLIC COMPOUNDS

CHAPTER 21

ALICYCLIC HYDROCARBONS AND THEIR DERIVATIVES

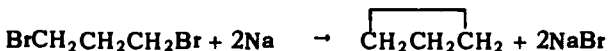
Modes of Formation

In this chapter, methods of synthesis of cyclic hydrocarbons as well as their derivatives have been considered. It is to be understood that the oxygenated or other derivatives may be converted to the corresponding parent hydrocarbons by use of the appropriate methods.

Many of the standard reactions lend themselves for the purpose of bringing about ring closure, and thus for the preparation of cyclic compounds from open chain compounds. Among these reactions are the Wurtz synthesis, ester condensation, Knoevenagel type of condensations and others. These will now be considered briefly.

Ring Formation by Wurtz Reaction

An example of the *Wurtz reaction* is afforded by the preparation of cyclopropane from α,γ -dibromopropane and sodium:¹



Cyclization may be brought about by use of zinc dust and 75% aqueous ethanol at 60°. ² Methylcyclobutane may be prepared similarly from α,δ -dibromopentane and sodium. ³

Yields of cyclopropane from secondary 1,3-dibromo derivatives are less than those from the primary derivatives, and least with tertiary derivatives. Yields are improved, however, when the reaction is carried out under mild conditions. ⁵¹⁸

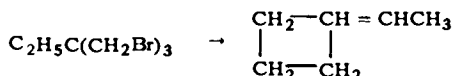
Cyclobutane and its homologs have been obtained in very low yield by this method from 1,4-dihalobutanes. A series of alkyl cyclobutanes have been made by treating neopentyl tribromides with zinc: ²⁶²



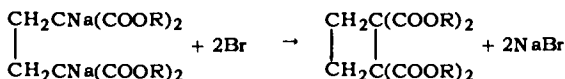
A hydrocarbon mixture with the empirical formula C_5H_8 has been obtained through the reaction of tetrabromotetramethylmethane, $\text{C}(\text{CH}_2\text{Br})_4$, and zinc dust in alcoholic suspension. It is composed principally of methylenecyclobutane, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, and methylcyclobutene, $\text{CH}_2\text{CH}_2\text{CH}=\text{CCH}_3$, and contains some spiropentane,



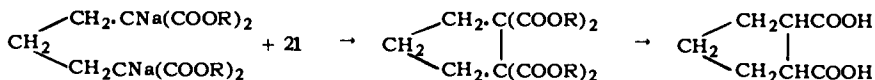
Spiropentane is formed in good yield when the tetrabromo compound is reduced with zinc in molten acetamide.⁵¹⁹ Conditions may be so adjusted as to obtain 2-methylbutene as the principal product of the reaction.⁵²⁰ Ethylenecyclobutene is formed as the principal product when 1,1,1-tri-(bromomethyl)propane is dehalogenated with zinc in acetamide.⁵²¹



Cyclobutane 1,1,2,2-tetracarboxylic ester has been prepared by the action of bromine on disodiobutanetetracarboxylic ester:



The free acid loses two molecules of carbon dioxide on heating, and is thereby converted to cyclobutane-1,2-dicarboxylic acid. Similarly, cyclopentane-1,2-dicarboxylic acid may be obtained from disodio cyclopentanetetracarboxylic acid and iodine:

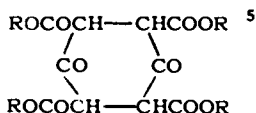


These open chain tetracarboxylic acids are obtained through the reaction of *sym*-di-bromoethane and α,γ -dibromopropane with malonic ester in the presence of metallic sodium.

Applied to the disodio derivative of acetonedicarboxylic ester,

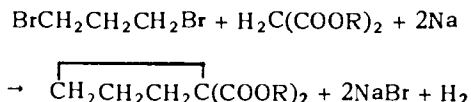


the reaction gives the cyclic diketotetracarboxylic ester



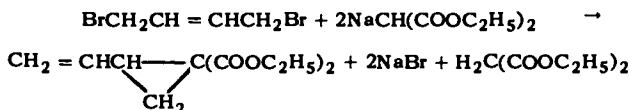
Ring Formation by Condensation of Halo Compounds with a Reactive Methylene Group

Ring closure may be accomplished through the reaction of dihalo compounds with compounds containing a reactive methylene group, in the presence of sodium alcoholate. Cyclobutanedicarboxylic ester is obtained, for example, through the reaction of 1,3-dibromopropane with malonic ester in the presence of metallic sodium:⁶

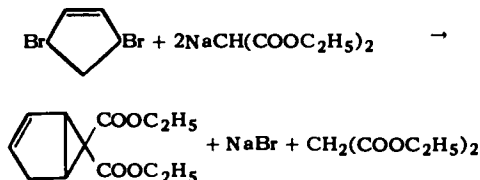


In the same manner ethylene dibromide and pentamethylene dibromide yield cyclopropane and cyclohexanedicarboxylic acids respectively.

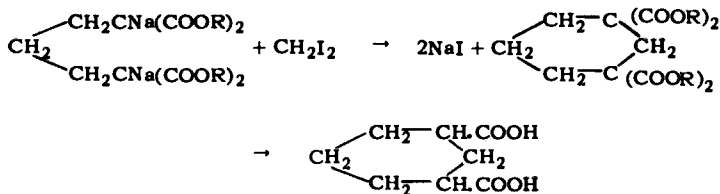
The reaction of 1,4-dibromobutene-2 with sodio malonic ester results in the formation of 2-vinylcyclopropane-1-dicarboxylic ester:^{5,22}



The reaction with *cis* or *trans* 1,4-dibromocyclopentene-2 similarly results in the formation of a bicyclo(3,1,0)hexane derivative:



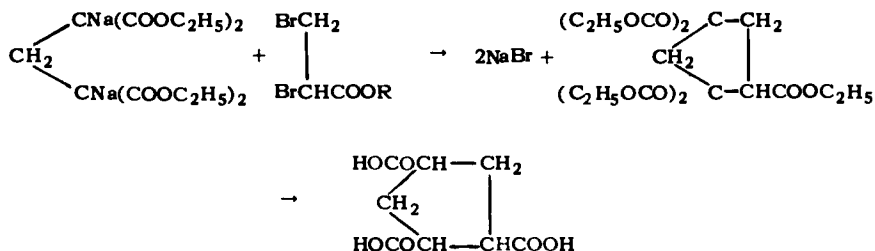
Cyclohexane-1,3-dicarboxylic acid has been prepared by the reaction of disodiopentametetracarboxylic ester with methylene iodide, and the subsequent hydrolysis and partial decarboxylation of the resulting tetracarboxylic ester:



1-Methylcyclopentane-2,2-dicarboxylic ester, $\text{CH}_3\text{CH}(\text{CH}_2)_3\text{C}(\text{COOR})_2$, has been obtained by this method from 1,4-dibromopentane.⁷ The free dicarboxylic acid is readily decarboxylated to 1-methylcyclopentane-2-carboxylic acid by heating a few degrees above its melting point.

1-Methylcyclopentane-2,3-dicarboxylic acid has been obtained by the reaction of 1,3-dibromobutane with disodioethane tetracarboxylate followed by the partial decarboxylation of the free tetracarboxylic acid.⁸

Cyclopentane-1,2,4-tricarboxylic acid has been obtained through the reaction of ethyl α,β -dibromopropionate with ethyl disodio propane- $\alpha,\alpha,\gamma,\gamma$ -tetracarboxylate, followed by the partial decarboxylation of the free pentacarboxylic acid:⁹

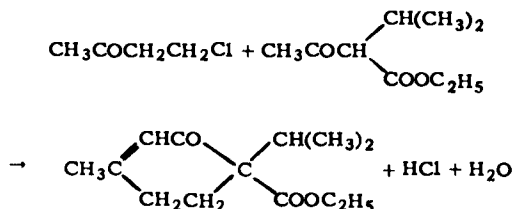


The acid exists in the *cis* and *trans* configurations.

Similarly *apofenchocamphoric acid* has been obtained from the same disodium tetracarboxylic ester and isobutylene dibromide, $(\text{CH}_3)_2\text{CBrCH}_2\text{Br}$, on hydrolysis and partial decarboxylation of the original reaction product.¹⁰

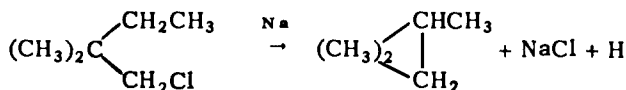
Cyclohexane-1,3-dicarboxylic acid has been prepared by this method from disodium pentanetetracarboxylic ester and methylene iodide, by hydrolysis and partial decarboxylation of the reaction product.

The formation of ethyl Δ^1 -*p*-menthen-3-one-4-carboxylate from β -chloroethyl methyl ketone and α -isopropylacetoacetic ester involves the reaction of a halo compound with the sodio derivative of the acetoacetic ester, and the condensation of a carbonyl group with a reactive methyl group:¹⁰



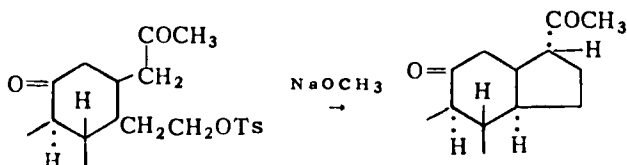
d-Piperitone results on decarboxylation of this compound.

Ring closure has been accomplished in some instances by dehydrohalogenation with sodium. Thus, 1,1,2-trimethylcyclopropane has been obtained from 1-chloro-2,2-dimethylbutane:²⁵⁷

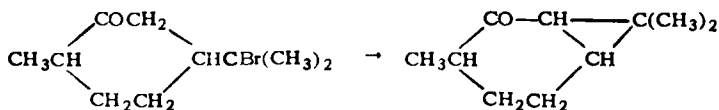


Methylcyclopropane has been similarly obtained from isobutyl chloride.²⁵⁸

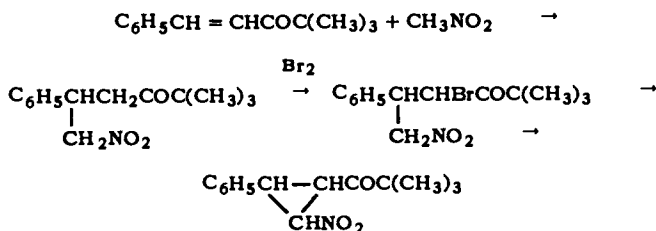
Tosylates may be employed instead of halides for the formation of a ring by internal condensation with a reactive methylene group, as has been done in the total synthesis of cortisone,³⁸⁴ cyclization producing ring D of the cortisone skeleton;



Carvestrene has been obtained by heating dihydrocarvone hydrobromide with alkali:⁴⁴

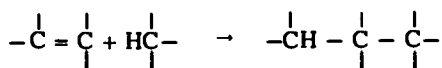


A number of nitrated cyclopropane derivatives have been made from the addition product of nitroethane and certain unsaturated compounds, by bromination followed by dehydrobromination.⁴⁵ The following is illustrative of the method:



Cyclizations Involving Addition at Unsaturated Bonds

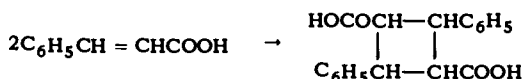
Union of carbon atoms may take place through a Michael type condensation which involves the addition of a hydrogen atom and an organic residue at the double bond:



This type of addition has been utilized extensively for the synthesis of a great variety of cyclic compounds.

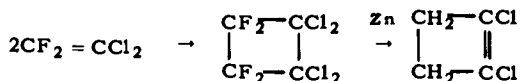
One of the simpler cases of ring closure based on this addition is the formation of *cyclopentadiene* from 1,3-pentadiene by passage through a tube heated at 600 to 620°. ²⁶⁰ Conversion per pass does not exceed 8%, but yields of up to 45% have been obtained by repeated passage of the unconverted open chain diene through the heated tube. The cyclopentadiene dimerizes readily and the dimer can be separated by distillation. ²⁶¹ The dimer can be partially depolymerized by distilling slowly in the presence of iron.

Another simpler case of cyclization by the Michael condensation is the formation of *truxilic acid* from *cinnamic acid*: ³²²

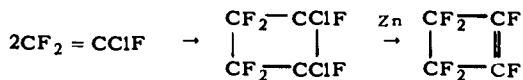


This is representative of numerous other dimerization reactions involving active double bonds that give rise to cyclobutane derivatives. Other examples are the dimerization of ketenes, allenes, fluoroolefins, etc. ⁵²³

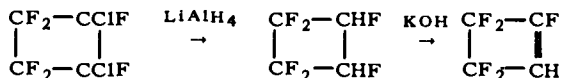
The dimerization of fluoroolefins offers an important method for the preparation of cyclobutane derivatives. ⁵²⁴ Thus, tetrafluorotetrachlorocyclobutane is formed from difluorodichloroethylene, and is converted by zinc to dichlorotetrafluorocyclobutane:



and hexafluorodichlorocyclobutane is formed from trifluorochloroethylene, and is converted to hexafluorocyclobutene with zinc:



The fluorine atoms attached to the unsaturated carbon atoms in the latter compound are replaceable with alkoxy and secondary amino groups. Reduction of the hexafluorodichlorocyclobutane with lithium aluminum hydride gives hexafluorocyclobutane which, on treatment with potassium hydroxide, is converted to pentafluorocyclohexene: ⁵²⁵



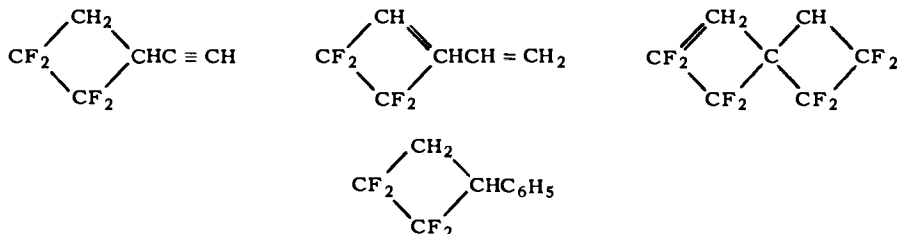
Tetrafluoroethylene is capable of adding to many unsaturated compounds to form cyclobutane derivatives, and the reaction often proceeds more readily than the polymerization of the fluoroethylene.⁵²⁶ With butadiene the following two compounds are obtained:



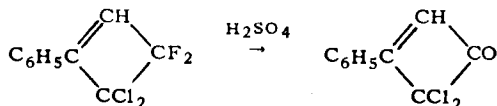
Allene gives methylene-2,2,3,3-tetrafluorocyclobutane and 1,1,2,2:5,5,6,8-octafluoro-spiro(3,3)heptane



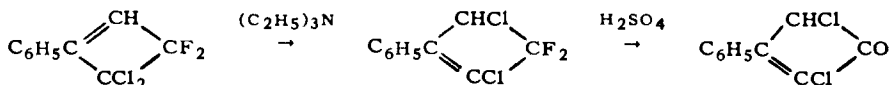
Reaction of tetrafluoroethylene with enynes may proceed with the participation of the ethylenic as well as the acetylenic linkage. Vinylacetylene yields the following compounds:



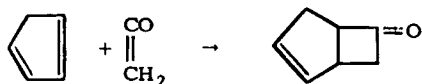
The last compound no doubt results through the reaction of tetrafluoroethylene with styrene formed by the partial polymerization of vinylacetylene. The adduct of phenylacetylene with tetrafluoroethylene has been converted to a series of halogen-free cyclobutane derivatives.⁵²⁷ The adduct of 1,1-difluoro-2,2-dichloroethylene and phenylacetylene, treated with concentrated sulfuric acid, is converted to 2,2-dichloro-3-phenylcyclobutane:



The adduct is isomerized by triethylamine to 2,4-dichloro-3,3-difluoro-1-phenylcyclobutane, which is converted by sulfuric acid to 2,4-dichloro-3-phenylcyclobutane:

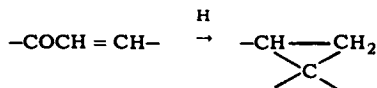


The cyclopropane ring may be formed through the addition of a ketene to an unsaturated linkage:⁵²⁸

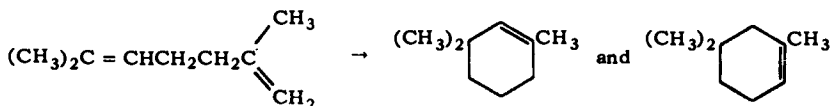


Sterols with an α,β -unsaturated carbonyl system in the ring may dimerize under the action of light with the formation of a fused four carbon ring.⁵²⁹

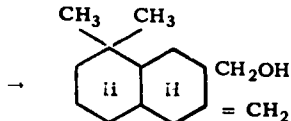
Formation of the cyclopropane ring has been observed in the Wolff-Kishner reduction of certain α,β -unsaturated ketones:⁵³⁰



Geranolene is cyclized under the influence of sulfuric acid to α - and β -cyclogeranolenes:⁵³³



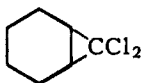
Sesquilandulol has been converted to a bicyclic dimethylmethyldene carbinol:⁵²⁶



Nerolidol has been cyclized to rac-ambreinolide after it was first converted to an acetic derivative.³²⁴ α -Bisabulene has been obtained by a similar cyclization of farnesene.³²⁵ Other similar condensations have been effected with farnesic, dihydro- α - and - β -ionylideneacetic acids and ω -geranylgeranic acid³²⁶ as well as the condensation product of farnesol with methyl isopropyl ketone in the presence of iodine.³²⁷

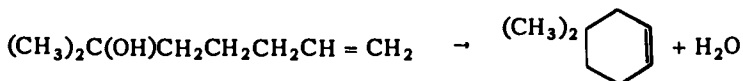
Compounds containing the system $-\text{CH}=\text{CHC}\equiv\text{CCH}=\text{CH}-$ have been cyclized under the action of hot formic acid to benzene derivatives.³²⁹

The reaction of potassium *tert*-butylate with chloroform results in the formation of dichlorocarbene, CCl_2 , which readily adds at olefinic bonds to form dihalocyclopropanes, cyclohexene, for example, giving 7,7-dichlorobicyclo(4,1,0)heptane,⁵³¹



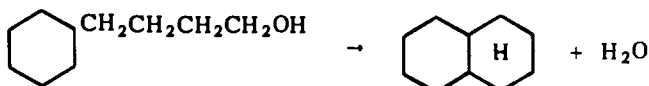
Bromoform behaves in a similar manner giving dibromocyclopropane derivatives.

Many olefinic alcohols have been converted to cyclic compounds. Cyclization is usually accompanied by the elimination of the elements of water and the formation of an unsaturated linkage. Tertiary methylheptenol with a terminal double bond has been cyclized to dimethylcyclohexene:³³⁰

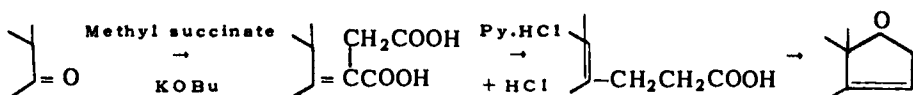


Nerolidol³³¹ and 1-methyl-2- Δ^7 -butenylcyclohexanol³³² have been cyclized to hexahydro and octahydronaphthalene derivatives.

Cyclizations may occur that involve a carbon atom in an aromatic nucleus and an unsaturated bond or an easily removable hydroxyl group in a side chain. 4-Phenyl-n-butanol treated with sulfuric acid gives tetrahydronaphthalene:³³³

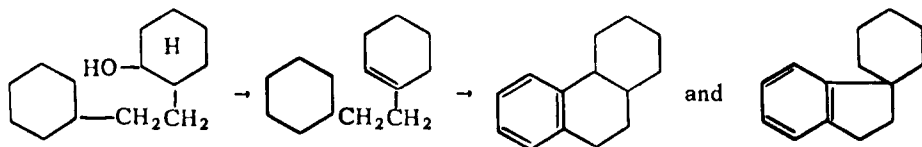


5-Phenyl-1,2-pentene gives methyltetrahydronaphthalene. 1- γ -Butenylcyclohexanol gives $\Delta(9:10)$ -octalin;³³⁴ 1- γ -butenyl-2-methylcyclohexanol yields a 9-methyloctalin and 9-methyldecalin.³³⁵ Benzene derivatives with unbranched side chains of five to seven carbon atoms containing a double bond or a hydroxyl group generally yield tetralin derivatives on treatment with sulfuric acid, except when the double bond or the hydroxyl group adjoin the phenyl group. Polymeric bodies are formed in the latter case. When the side chain carries a methyl group in position 3 to the phenyl group, derivatives of indane and tetralin are formed simultaneously. Ring formation may take place by the addition of an acyl group at an unsaturated bond and removal of elements of water. This has been accomplished, for example, in the synthesis of Δ^{14} -equilenin methyl ether from 2-methyl-7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene by a stobbe condensation with succinic ester followed by decarboxylation and cyclization.³⁸⁵

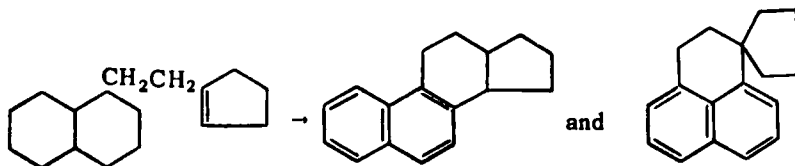


Bogert and Cook Synthesis

In this method, a cyclic alcohol bearing an aryl ethyl group is treated with a mild dehydrating agent, and the resulting unsaturated body is cyclized with sulfuric acid. A spiro compound is formed, together with the normal polycyclic body:³³⁶



The method has been employed for the preparation of tetracyclic compounds.³³⁷ Cyclopentanetetrahydronaphthalene is obtained from β -naphthylethylcyclopentene together with a spirohydrocarbon:

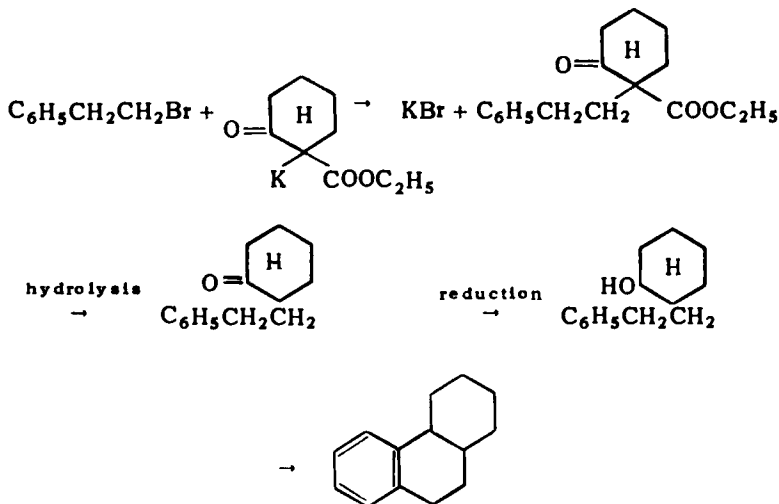


A spiran is not formed if a methyl group is attached to the carbon atom bearing the hydroxyl group in the cyclic alcohol.³³⁸ Cyclization may be brought about with aluminum chloride.

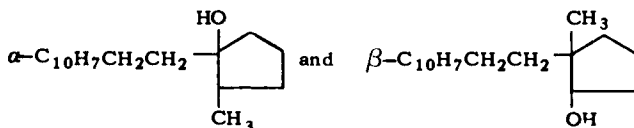
Molecular rearrangements may occur in the course of the reaction. The condensation product of β -phenylethylmagnesium bromide and cyclohexene oxide, for example, is β -phenylethylcyclopentyl carbinol.³³⁹

*Bardhan-Sengupta Method*³⁴⁰

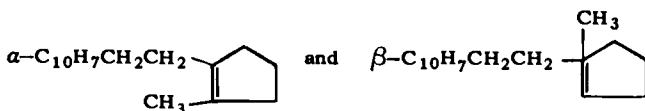
This method is similar in its general lines to the Bogert-Cook synthesis. The aryl ethyl cyclic alcohol is prepared through the reaction of the potassium compound of a cyclic ketone with a halogenated body, and the resulting ketone is reduced to the corresponding alcohol. The latter is then cyclodehydrated by heating at 140° with phosphoric oxide:



It is of interest to note that while both of the naphthyl derivatives



yield the angularly 18-methylated cyclopentanophenanthrene, of the unsaturated derivatives

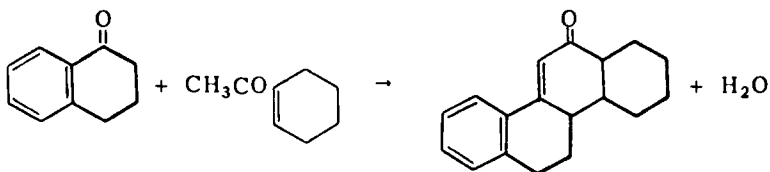


obtained by the dehydration of the hydroxy compounds, only the second undergoes cyclization to form the isomeric 14-methylated cyclopentanophenanthrene derivative.³⁴¹

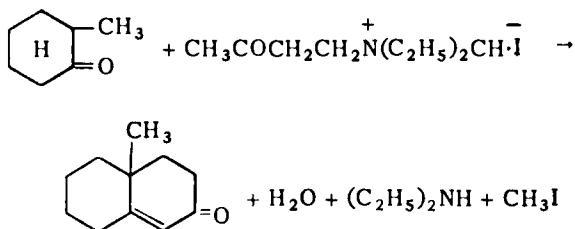
The Bardhan-Sengupta method of cyclization has been applied successfully to esters of cyclic hydroxy acids. Many unsaturated hydroaromatic ketones cannot be cyclized by this procedure.³⁴²

Rapson-Robinson Synthesis

This method of ring formation involves the condensation of a methyl group with a carbonyl group and a coupling at an unsaturated bond.³⁴³ An example is offered by the formation of a ketodecahydrochrysene from α -tetralone and acetylcyclohexene:



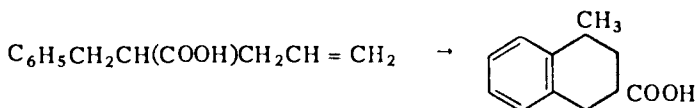
The unsaturated bond need not be present originally in the cyclizing component, but may be formed during the reaction, as in the following example:



The method has been employed in the total synthesis of \pm cortisone from 5-methoxy-2-tetralone.³⁸⁶

Darzens Synthesis

The simplest example of this synthesis is presented by the cyclization of benzylallylacetic acid under the action of 78% sulfuric acid below 45°.³⁴⁴



A γ -lactone, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{COO})\text{CH}_2\text{CHCH}_3$ is also formed simultaneously, which can be slowly cyclized by heating at 120° with 65% sulfuric acid.³⁴⁵ Unlike γ -lactones, δ -lactones fail to cyclize to tetralin derivatives. Benzylallylacetic acid is obtained from malonic ester by successive benzylation and allylation, followed by hydrolysis and partial decarboxylation.

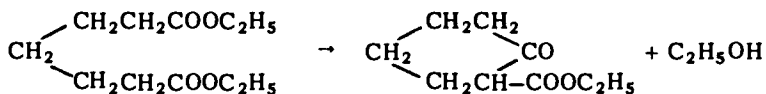
The reaction seems to be of general applicability. Substituted phenylethylallylacetic acids with a methyl, isopropyl, tertiary butyl, and methoxy groups in the para position in the phenyl group undergo this cyclization.³⁴⁶ Benzyl dimethylallylacetic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{COOH})\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ fails to undergo cyclization,³⁴⁷ although the carbinol $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)_2$ may be cyclized by dehydration. Phenylmethallylacetic acid,



undergoes cyclization slowly.³⁴⁸ The method has been applied to the synthesis of hydrophenanthrene derivatives.³⁴⁹

Cyclization by Bouveault-Dieckmann Ester Condensation

Ring formation may be brought about through intermolecular *ester condensation* of a dicarboxylic ester. Thus, the internal condensation of pimelic ester leads to the formation of cyclohexanone carboxylic acid:

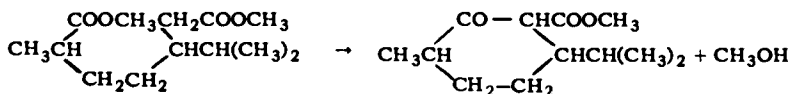


Similarly, five and seven carbon ring cyclic ketocarboxylic acids result from diethyl adipate and diethyl suberate.

A fused four membered ring has been obtained through an internal acyloin condensation of hexahydrophthalic diethyl ester in dilute xylene solution under the action of metallic sodium.

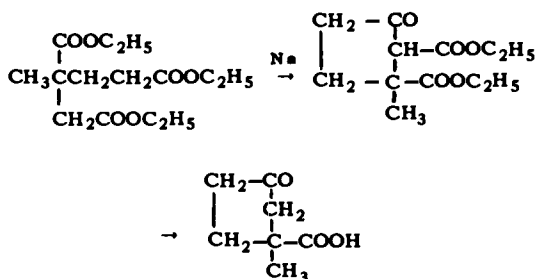
Succinic ester condenses under the influence of metallic sodium into a six carbon ring, succino succinic ester, hydrolysis of which gives a cyclic diketone; the latter may be reduced to cyclohexane by first converting it to the corresponding dihydric alcohol, then to the corresponding diiodide, and finally reducing this with zinc dust and acetic acid.

An internal ester condensation is the first step in a method of synthesis of carvomenthone:¹¹



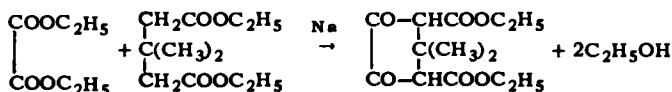
hydrolysis of the keto carboxylic acid and decarboxylation giving the desired compound.

Ester condensation is involved as a step in the preparation of 3-methylcyclopentanone-3-carboxylic acid, employed in the complete synthesis of fenchone:¹²



The tricarboxylic ester required for this synthesis was obtained by Reformatsky's reaction from bromoacetic ester and levulinic ester.

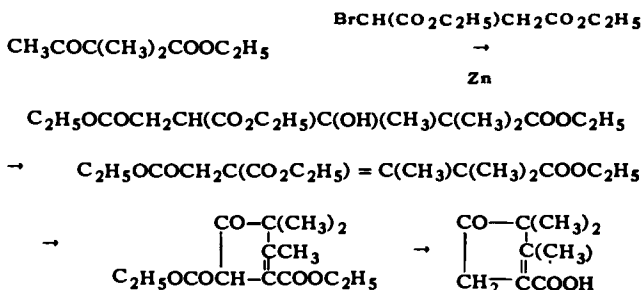
The cyclic diketone resulting through the condensation of ethyl oxalate with ethyl β,β -dimethylglutarate has served as the starting point for the synthesis of camphoric acid;¹³



The synthesis involves methylation and reduction of the carbonyl groups. *Apocamphoric acid* has been prepared from the original condensation product by reduction.¹⁴

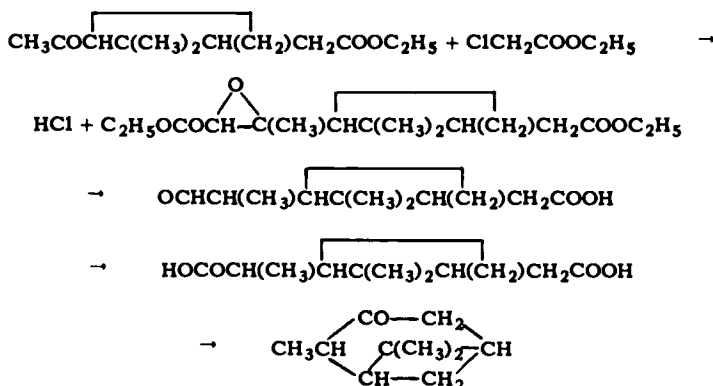
The condensation product of oxalic ester with β -methylglutaric acid has similarly served as the starting point for the synthesis of allosantenic acid, the process involving substantially the same steps.¹⁵

Ketoisolaurolic acid has been obtained by ester condensation followed by decarboxylation from the dehydrated condensation product of dimethylacetoacetic ester and bromosuccinic ester in the presence of zinc:



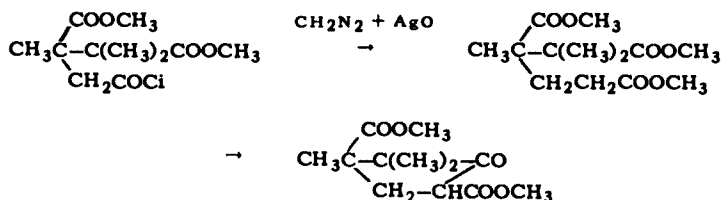
Isolaurolene, $\text{CH}_2\text{CH}_2\text{CH} = \text{C}(\text{CH}_3)\text{C}(\text{CH}_3)_2$, has been obtained from this by reduction with zinc and hydrochloric acid, followed by bromination with alkali and heating the resulting isolaurolenic acid under pressure at 300° .¹⁶ Isolaurolene can be isomerized to laurolene by distilling a mixture of the hydrocarbon with anthracene.

Pinocamphone has been synthesized from ethyl *dl*-pinonate by reaction with chloroacetic ester in the presence of sodium, hydrolysis of the resulting oxidoester to the acid, conversion of the latter to an aldehyde acid by heating in vacuum, oxidation of this to the corresponding dicarboxylic acid, and finally cyclization of the ester of the latter under the action of metallic sodium:⁴⁶



A similar synthesis of thujone carboxylic acid has been carried out starting with thujaketic acid.⁴⁷ Heated with barium hydroxide thujone carboxylic acid is converted to thujone.

When trimethyl camphorionate is partially hydrolyzed, the primary ester group undergoes preferential saponification. The chloride of the resulting ester acid treated with diazomethane and silver oxide gives trimethyl homocamphorionate, which undergoes cyclization when treated in benzene solution with zinc and a trace of alcohol, giving 2,2,3-trimethylcyclopentanone-3,5-dicarboxylate:



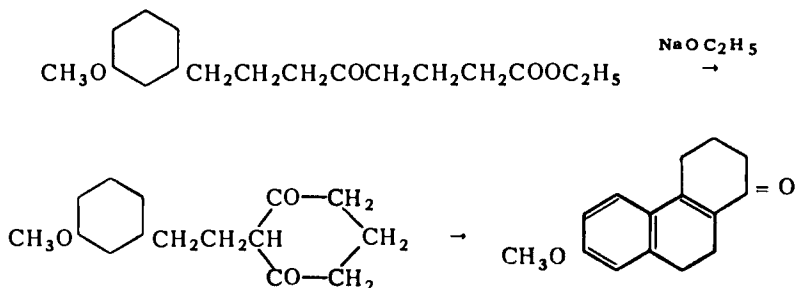
6-Methoxynaphthalene-1-(α -methyl)butyric acid has been cyclized to 1-keto-7-methoxytetrahydrophenanthrene. When the latter is condensed with β -bromopropionic ethyl ester by Reformatsky's method, and the product, after dehydration and conversion to the acyl chloride is cyclized, 3-methoxy-18-methyl-17-keto cyclopentanophenanthrene is obtained.

d-Equilenin has been prepared from the ester of the 3-carboxy-4-propionic acid of a methoxy phenanthrene by an internal Dieckmann condensation, followed by hydrolysis, decarboxylation and demethylation.⁵¹⁵ The Dieckmann condensation has been employed in the Cornforth-Robinson synthesis of cholesterol from 3-methoxy-1-methyl-3-tetralone. A Dieckmann condensation was involved also in the total synthesis of oestrone-a.³⁸⁷

In the *Robinson-Schlitter method*, the keto esters

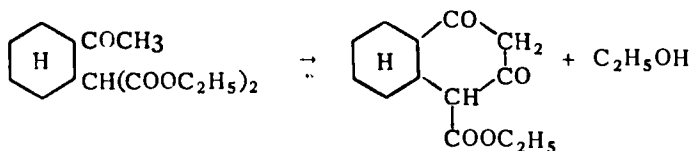


are first condensed to diketocyclohexanes and these are further cyclized by dehydration with phosphorus pentoxide.³⁵⁰



The intermediate keto ester is obtained by the reaction of an arylbutyryl chloride with ethyl sodio α -acetylglutarate.

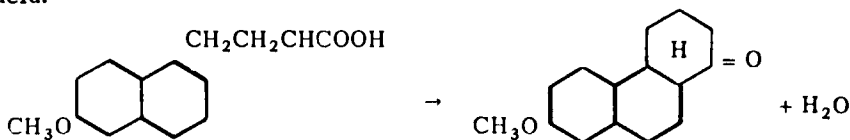
Bougault's synthesis involves an ester condensation as the last step:



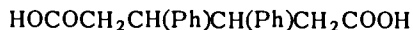
The acetylcyclohexylmalonic ester and other similar intermediates required for the synthesis are prepared by a Michael condensation of a cyclohexene and malonic or other ester with a reactive methylene group.³⁵¹

Ring Formation by Cyclodehydration of Acids

The terminal carboxyl group in a four carbon chain attached to an aromatic nucleus may be condensed with the aromatic ring under certain conditions to form a new six-membered ring. For example, 6-methoxynaphthalene-1-butyric acid may be cyclized to a tricyclic ketone under the action of 90% sulfuric acid.³⁵²



Meso and racemic β,γ -diphenyladipic acids

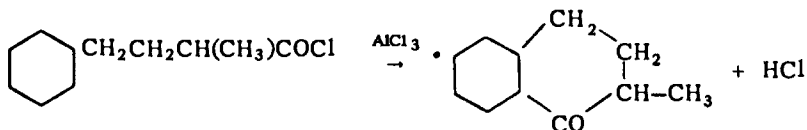


are readily cyclized by hot 85% sulfuric acid.³⁵³ Bis(O-methylphenyl)glutaric acid, $(\text{CH}_3\text{C}_6\text{H}_4)_2\text{CHCH}(\text{CH}_2\text{COOH})_2$ has been cyclized to 5,4-dimethyl-3,4-benzophenanthrene.³⁵⁴

Retene has been prepared by cyclizing 3-(6-isopropylmethyl-2)-*n*-valeric acid followed by dehydrogenation with selenium.³⁵⁵ *Pimanthrene* has been obtained similarly from 3-(6-methylnaphthyl-2)-*n*-valeric acid.

A number of other cyclizations have been effected by this method.³⁵⁶ Cyclization may be brought about also with hydrogen fluoride.³⁵⁷

Cyclization of an acid is often accomplished through the intermediary of the acid chloride. A typical example is the formation of α -hydrindene from the chloride of α -methyl- γ -phenylbutyric acid:³⁵⁸



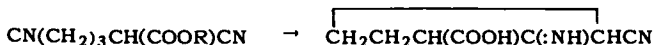
The acids required for this synthesis may be obtained by condensing substituted succinic anhydrides with aromatic hydrocarbons and subsequently reducing the acid obtained by Clemmensen's method. They may be prepared also through the condensation of bromoaromatic ketones, such as ω -bromoacetophenone with sodio malonic esters and subsequent reduction, hydrolysis and partial decarboxylation. Five membered rings have also been synthesized by this method. The method has formed the basis for the synthesis of a large variety of naphthalene and phenanthrene derivatives.³⁵⁹

In competitive reactions, the tetralone system is formed more readily than the hydrindone and this more readily than the benzsuberone system.³⁶⁰

Cyclohexenylbutyryl chloride in carbon disulfide solution has been cyclized to 1-ketooctahydronaphthalene at -7 to -10° in the presence of tin tetrachloride.³⁶¹

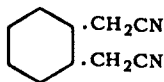
Thorpe's Reaction¹⁷

Thorpe's reaction applied to dicyano compounds leads to the formation of a cyclic compound in a manner resembling ester condensation. Dicyanovalepic ester, for example, undergoes internal condensation under the influence of sodium ethoxide, to give a cyclic imino compound:



On hydrolysis with sulfuric acid, this compound is converted to the corresponding keto dicarboxylic acid, and this in turn gives cyclopentanone on decarboxylation.

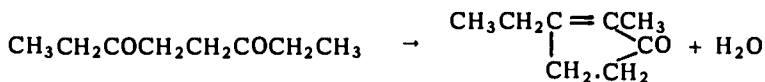
Adiponitrile, $\text{CN}(\text{CH}_2)_4\text{CN}$, undergoes the Thorpe reaction readily. The aromatic dinitrile



also undergoes condensation with ease.¹⁸

Ring Formation by Condensation of Carbonyl Groups with Reactive Methylene Groups

Condensations involving a carbonyl group and a reactive methylene within the same molecule also may lead to ring formation.²⁴³ The conversion of *sym*-dipropionylethane to 1-methyl-5-ethyl- Δ^5 -cyclopentene-2-one¹⁹ is representative of this type of reaction:



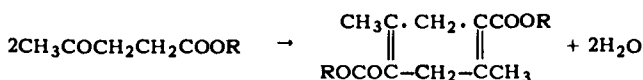
The formation of isophorone apparently comes about through this type of condensation.

The diketone obtained through the ozonolysis of octalin undergoes a similar condensation under the action of sodium carbonate giving cyclopentenocycloheptanone;²⁶⁴

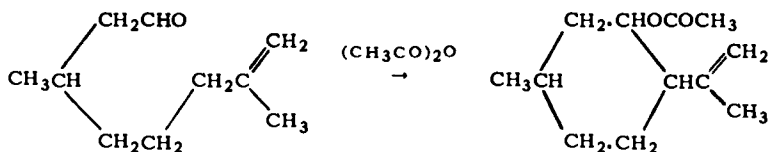


The ketone has served as the starting point for the preparation of 4-substituted azulenes.

The condensation of two molecules of levulinic ester to a cyclopentadienedicarboxylic ester may be cited as another example:²⁰

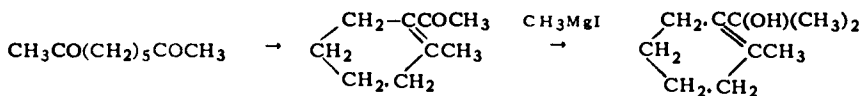


Isopulegol acetate has been obtained by this method through the internal condensation of citronellol in the presence of acetic anhydride;²¹

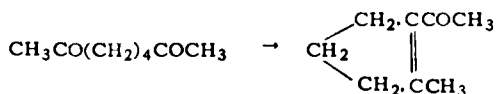


Pulegone has been prepared from the corresponding alcohol, by oxidation followed by isomerization.

The synthesis of Δ^1 -*o*-menthol has been effected from diacetylpentane by condensation to methyl methylcyclohexyl ketone in the presence of sulfuric acid followed by reaction with methylmagnesium iodide:



Methylcyclopentane methyl ketone results through the condensation of diacetylbutane under the action of sulfuric acid:²²

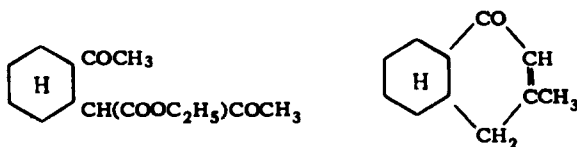


Methylheptenone may be condensed to 1,3-dimethyl- Δ^3 -cyclohexene under the influence of dehydrating agents, *m*-xylene being also formed in the reaction.²²

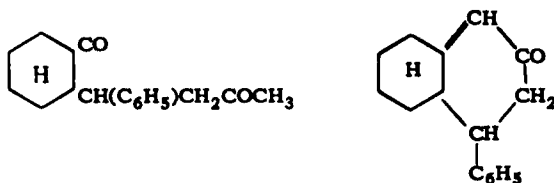
Acetylacetone and acetylacetophenone do not undergo internal ring condensation of this type.

Methyl cyclohexanone-2-ethyl ketone has been cyclized to a 2-ketooctahydronaphthalene.³⁶³

The condensation product of acetylcyclohexene with ethyl sodio acetoacetate has been converted to an unsaturated ketone by internal condensation.³⁶⁴

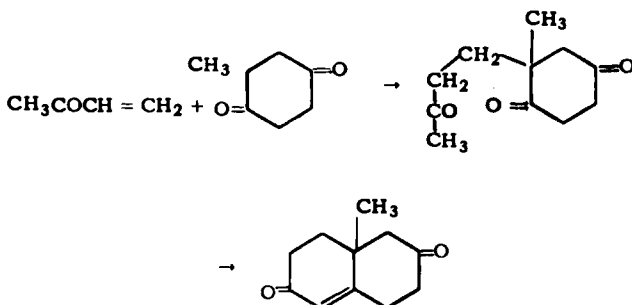


The condensation product of sodio cyclohexanone and styryl methyl ketone undergoes cyclodehydration to a 2-keto-4-phenyloctahydronaphthalene:³⁶⁵



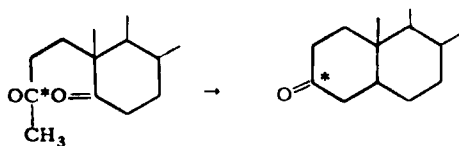
The method is of general applicability, and has been employed for the preparation of hydrophenanthrones.³⁶⁶

A diketooctahydronaphthalene which has served as an intermediate in the synthesis of cortisone has been prepared by the condensation of methyl vinyl ketone with dihydro-2-methylresorcinol.³⁶⁷ The reaction involves an addition at a double bond, followed by the condensation of a methyl group with a keto group:

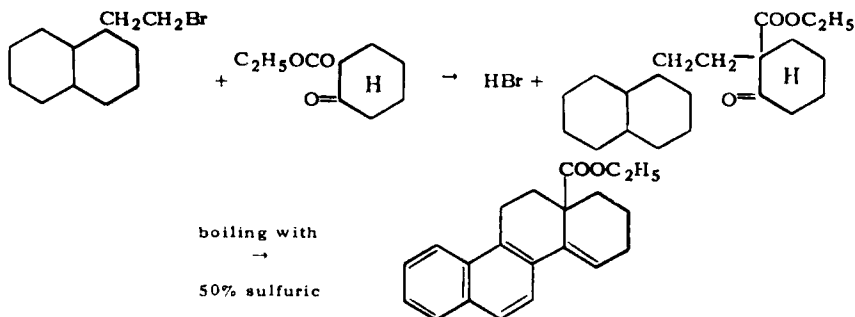


Steps involving condensation with ethyl vinyl ketone and acrylonitrile form the route to a synthesis of cortisone.³⁶⁸ In this as also in the synthesis of Windaus acid³⁶⁹ one position in the molecule was protected by the introduction of a methylanilinomethylene group prior to reaction with acrylonitrile.

The radioactive carbon atom has been introduced into the molecule of cholestenone by converting this compound by cleavage of ring A to a keto acid, reacting the latter with radioactive phenyl acetate, isolating, hydrolyzing and decarboxylating one of the two compounds formed, and cyclizing the resulting diketone to cholestenone, which contains a radioactive carbon at the position indicated by an asterisk,³⁷⁰



The keto ester $C_6H_5CH_2CH_2CH(COOC_2H_5)COCOC_2H_5$, resulting from the condensation of ethyl γ -phenylbutyrate with ethyl oxalate may be cyclized to a dihydronaphthalene dicarboxylic acid. A sterol-like skeleton has been synthesized by a similar condensation from naphthalene-1-ethyl bromide and cyclohexanone-2-carboxylic acid.³⁷¹



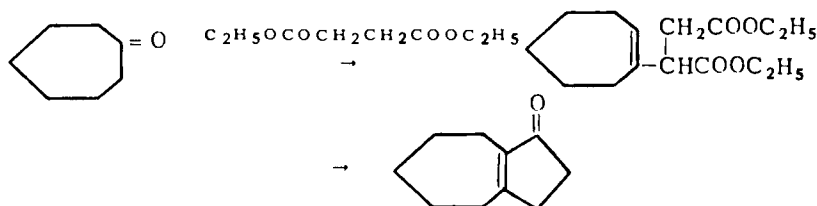
Dihydrophenanthrene-1-propionic-2-carboxylic acid has been prepared by this method from the condensation product of naphthylethyl bromide with the sodium derivative of β -keto adipic ester.³⁷² The compound, subjected to an ester condensation and decarboxylated, gave an α -ketone resembling equilin. Other similar syntheses have been carried out by this method.³⁷³ A like ketone condensation has been utilized in the synthesis of bisdehydrodisynolic acids and related compounds.³⁷⁴

The diketo acid, $C_6H_5COCH_2CH_2COCH_2CH_2COOH$, obtained by the hydrolysis of furfurylideneacetophenone, has been converted to 1-keto-4,5-benzohydrindene by a double cyclization involving the condensation of a carbonyl group with a methylene group, and a cyclodehydration.³⁷⁵

Large ring compounds with fused six-membered rings with a meta bridge are formed through the condensation of nitromalonaldehyde with cyclic ketones with eight or more carbon atoms in the ring.³⁷⁶

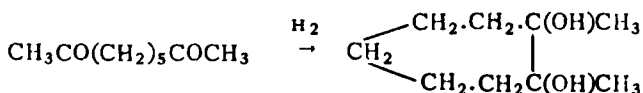
Stobbe Condensation

Cycloheptanone and succinic ester subjected to the *Stobbe condensation* give a dicarboxylic ester which on cyclization and decarboxylation gives bicyclo-(5,3,0)-dec-1(7)en-10-one:²³



A Stobbe condensation is involved in the formation of equilin from 2-methoxy-6-propionynaphthalene.²⁵⁸

Ring closure may occur by internal *pinacone condensation* involving two carbonyl groups in the same molecule. 1,2-Dimethyl-1,2-dihydroxycycloheptane may, thus, be obtained from diacetylpentane:²⁴



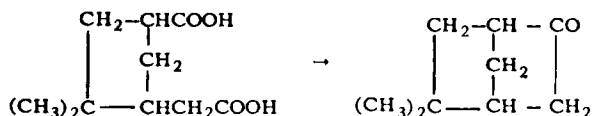
Formation of Cyclic Ketones from Dicarboxylic Acids

The method of preparation of ketones from metallic salts of acids, applied to dicarboxylic acids, leads to the formation of cyclic ketones. The formation of methylcyclopentane-2-one from the calcium salt of β -methyladipic acid is a typical example. The three carbon ring cannot be formed by heating calcium succinate, and the four carbon ring is formed in rare instances; cyclobutane cannot be obtained from calcium glutarate. The presence of a gem methyl group, $\text{C}(\text{CH}_3)_2$, in the molecule favors the formation of the cyclic ketone.

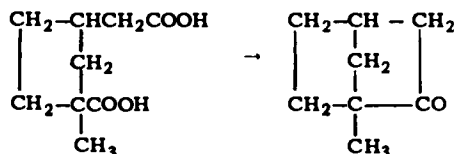
Calcium salts of higher normal dicarboxylic acids are converted to cyclic ketones in varying yield when subjected to dry distillation. Dicarboxylic acids with fewer than six carbon atoms in the chain yield anhydrides (*Blanc's rule*). Five membered rings are obtained in excellent yield, generally exceeding 80%; six membered rings in about 70%, seven membered rings in 50% yield. Eight membered rings are formed in 20% yield, while the nine to twelve membered rings are obtained in yields of a few tenths to 1%. Yields increase again, to about 5%, for the 15 and 16 membered rings.³⁷⁸ When the reaction is applied to long chain acids, it is of advantage to use the thorium, thallium, cerium or yttrium salts.³⁷⁹ Cyclization is brought about by distilling the salts under vacuum. Cyclic ketones have been prepared from the thorium salts of azelaic and sebacic acids, the yttrium salts of nonane and dodecane, ecosan- and octacosane- α,ω -dicarboxylic acids, and the thorium salts of pentadecane-, octadecane- and nonadecane- α,ω -dicarboxylic acids. Methyl groups and double bonds in the α -position to the carboxyl group hamper or prevent ring closure.

Trimethyl cyclopentadiene has been obtained by distillation of calcium α - or β -camphylate. Wandering of a methyl group or a double bond occurs during the transformation.³⁸⁰ Ring closure may be brought about without isomerization by heating the acid in quinoline in the presence of copper chromate. 1,1,2-Trimethyl-2,4-cyclopentadiene is then the product of cyclization.

The method has been applied to the synthesis of certain terpenes. Thus, *fencho-camphorone* has been obtained by heating the lead salt of the dicarboxylic acid derived from 5,5-dimethylcyclohexanone-3-carboxylic ester by condensation with cyanacetic ester, and subsequent reduction and hydrolysis:²⁵

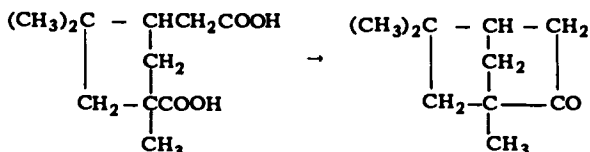


Similarly, 1-methylnorcamphor has been obtained by distilling the lead salt of the dicarboxylic acid derived from 3-methylcyclopentanone-3-carboxylic ester and bromoacetic ester through Reformatsky's reaction, followed by dehydration with phosphorus tribromide and reduction:



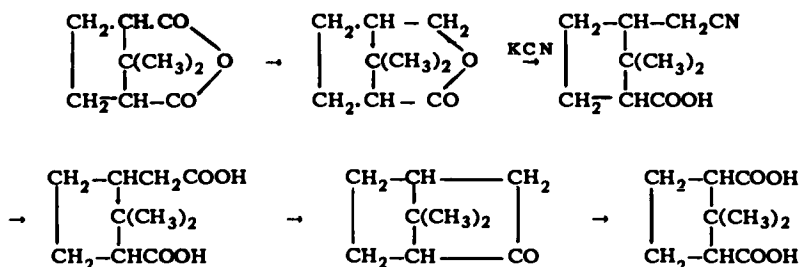
Fenchosantenone and *fenchone* have been obtained by methylating norcamphor with methyl iodide and sodium amide.

Isocamphor has been prepared from homoisofenchocamphoric acid by heating with barium hydroxide:²⁶

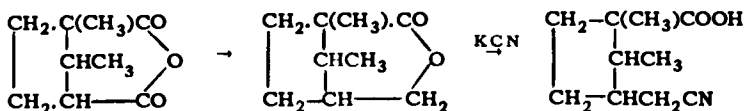


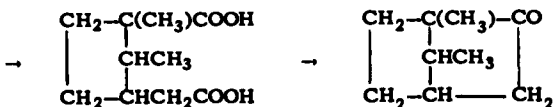
The homoisofenchocamphoric acid was obtained from 2,2,4-trimethylcyclohexanone-4-carboxylic ester by condensation with cyanacetic ester, hydrolysis, and partial decarboxylation.

The synthesis of *cis* and *trans*-apocamphoric acids has been accomplished starting from the condensation product of the ethyl esters of oxalic and dimethylglutaric acid. After complete reduction of the keto groups, the anhydride of the resulting acid was first converted to a lactide by reduction with sodium and alcohol, the lactide being then reacted with potassium cyanide. Hydrolysis of the resulting nitrile and distillation of the lead salt of the dicarboxylic acid obtained gave a bicyclic ketone. Oxidation of the latter resulted in the formation of apocamphoric acids.¹⁴



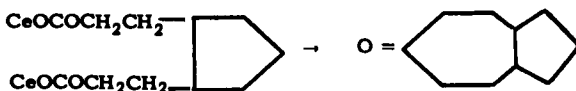
Santenone has been synthesized from *santenic* anhydride by hydrogenation to *santolide*, followed by treatment with potassium cyanide to obtain *homosantenonitrile*. Hydrolysis of this to the corresponding dicarboxylic acid followed by distillation of the calcium salt of the acid results in the formation of *santenone*.²⁷



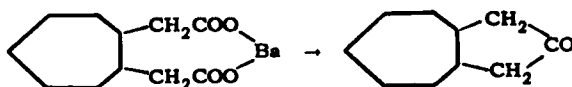


A cyclic diketone, $\text{COCH}_2\text{CH}_2\text{COCH}_2\text{CH}_2$, results on heating calcium succinate.

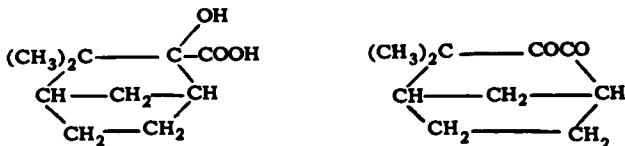
The cerium salt of *cis* or *trans* cyclopentane-1,2-dipropionic acid gives on distillation *cis* or *trans* bicyclo (5,3,0)-decane-4-one:



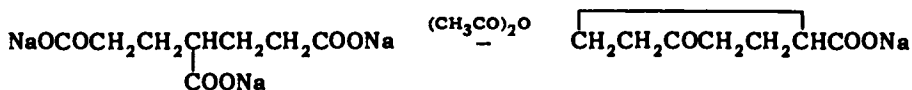
The barium salt of cycloheptanone-1,2-diacetic acid gives, on pyrolysis, bicyclo (5,3,0)-decane-9-one,



The lead salt of camphenylic acid gives on distillation carbocamphenilone:²⁹



Cyclic ketones may be obtained by heating the anhydrides of dicarboxylic acids at 300°. ³⁷⁸ Adipic and pimelic anhydrides and their alkyl substituted derivatives are converted to cyclic ketones with loss of carbon dioxide when they are distilled under ordinary pressure. ³⁸¹ A cyclic ketone has been obtained by treating the sodium salt of pentane- α - γ - ϵ -tricarboxylic acid with acetic anhydride: ²⁸

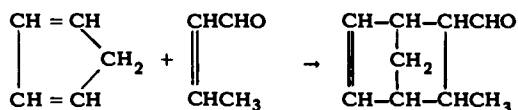


This ketone has served as the starting point for the complete synthesis of limonene.

Formation of Cyclic Compounds by Diene Synthesis

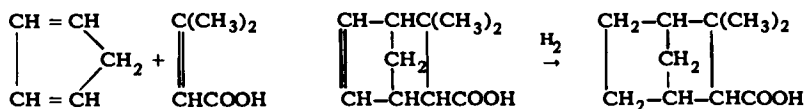
Numerous important ring syntheses have been achieved by the *Diene synthesis*. They have been considered in Chapter XX dealing with that subject. A few examples suffice to illustrate the method.

The condensation of cyclopentadiene and crotonaldehyde results in the formation of a dicyclic aldehyde: ³⁰

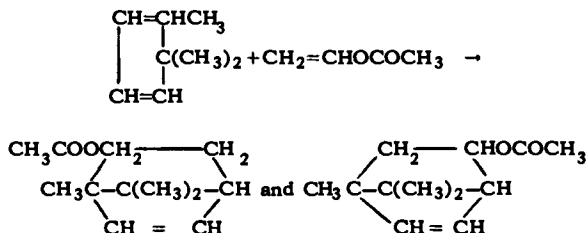


3-Methylnorcamphor has been prepared from this aldehyde by reduction, conversion to an enol acetate, and finally ozonolysis of the hydroxymethylene acetate obtained. 3-Methylnorcamphor, in turn, has served as the starting point for the synthesis of santene, which was accomplished by reaction with methylmagnesium iodide, and dehydration of the alcohol obtained by the hydrolysis of the resulting magnesium compound.

Isocamphanilic acid has been prepared from the condensation product of cyclopentadiene and dimethylacrylic acid, by reduction of the unsaturated bond:³¹



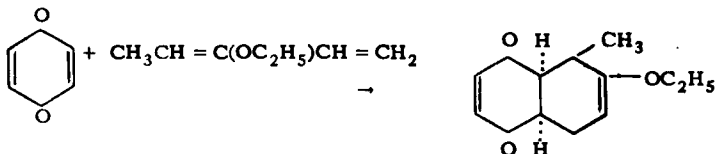
The condensation product of vinyl acetate and 1,5,5-trimethyl- $\Delta^1,3$ -cyclopentadiene has been utilized for the synthesis of borneol and epiborneol:³²



Reduction of these compounds followed by saponification gives borneol and epiborneol.

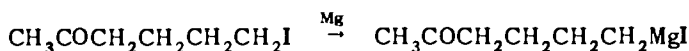
Many syntheses of polynuclear compounds have been effected by use of the Diene condensation.²⁶⁵

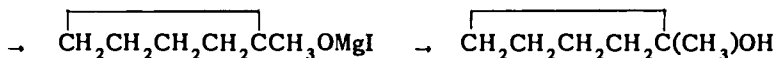
Condensation of benzoquinone with 3-ethoxypenta-1,3-diene gives a dihydroxy derivative of naphthalene which has served as an intermediate in a synthesis of cortisone:³²⁸



Ring Formation by Use of the Grignard and Friedel-Crafts Reactions

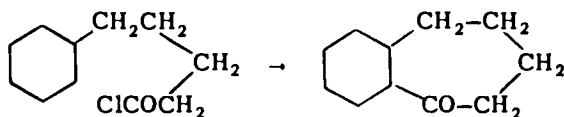
The Grignard reaction may be utilized for the purpose of ring formation, if a reactive halogen and a group reactive toward Grignard reagents, such as carbonyl are present in the molecule. Thus, methyl 4-iodobutyl ketone, treated in ethereal solution with magnesium powder, gives the magnesium derivative of 1-methyl-1-hydroxycyclopentane:³³





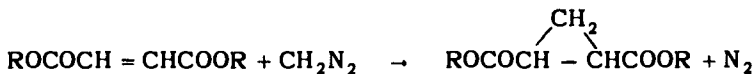
The Grignard reaction has been used for the introduction of methyl groups in unsaturated cyclic compounds, such as cadinene, by first epoxidizing these.²⁶⁶

Friedel-Crafts reaction has also been utilized for the purpose of ring formation. Thus, phenylvaleryl chloride subjected to the reaction is converted to benzocycloheptanone:

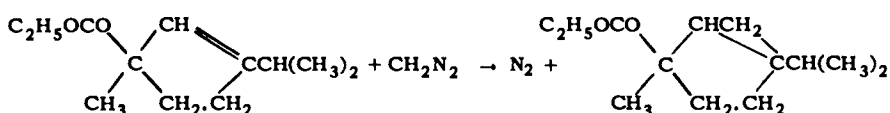


Ring Formation with Diazo Compounds

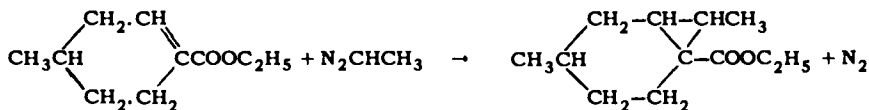
The cyclopropane ring can, in many cases, be established through the reaction of an aliphatic diazo compound with an ethylenic linkage. Cyclopropane dicarboxylic acid results, for example, through the reaction of diazomethane with fumaric acid:³⁴



dl-Thujane has been synthesized from 1-methyl-2-isopropylcyclopentene-1-carboxylic ester and diazomethane:³⁵

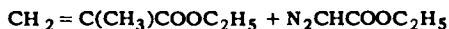


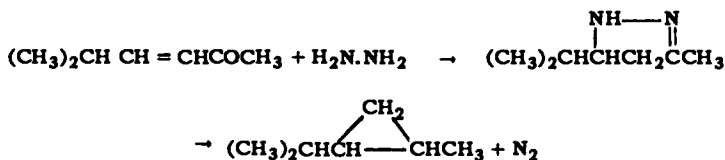
the hydrocarbon resulting through the decarboxylation of the free acid. The unsaturated acid is derived from methylisopropylcyclopentanone-1-carboxylic ester by reduction to the corresponding alcohol with sodium amalgam, and subsequent dehydration with phosphorus pentoxide. *dl*-Carane has been synthesized from 4-methylcyclohexene-1-carboxylic ester by reaction with diazomethane:³⁶



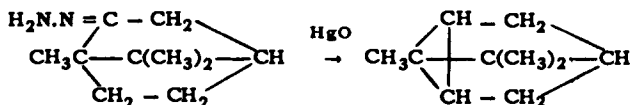
decarboxylation of the free acid yielding the hydrocarbon. The unsaturated acid was prepared in this instance from 4-methylcyclohexanone via the cyanhydrin obtained by reaction with hydrocyanic acid in the presence of a trace of a base, and hydrolysis to acid and dehydration.

Diazoacetic ester reacts in the same manner as diazomethane, reaction with ethyl isopropylacrylate, for example, leading to the formation of 1-isopropylcyclopropane-1,2-carboxylic ester:³⁷





Three carbon ring formation has been induced by heating camphorhydrazone with yellow mercuric oxide in alkaline solution, the reaction resulting in the formation of tricyclene:³²



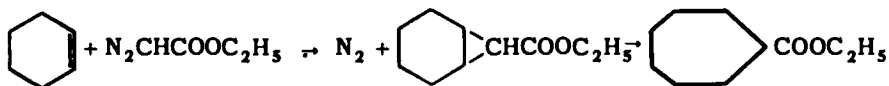
This is the most convenient method for the preparation of tricyclene. A similar treatment of *trans-n*-hydroxycamphorhydrazone results in the formation of *dl*-teressantol.⁴³

Methods of Ring Expansion

Ring Expansion by Use of Diazo Compounds

Aliphatic ketones are converted to their next higher homologs by reaction with diazomethane in solution in certain polar solvents in the presence of catalysts.³⁸⁸ The reaction has been extended to cyclic ketones;³⁸⁹ it fails to proceed smoothly and epoxides are always formed as by-products. Cycloheptanone is formed in 63% yield; it is converted to cyclooctanone by further reaction with diazomethane, but conversion of cyclooctanone to the next higher homolog proceeds with difficulty. Cyclic ketones having fifteen or more carbon atoms in the ring react well.³⁹⁰ The method has been applied with success to 2-chloro and 2-phenylcyclohexanone.³⁹¹ Reaction proceeds vigorously with camphorquinone and results in the formation of 4-methoxy-3,4-dehydrohomocamphor together with a liquid stereoisomer. Other diazo compounds have been used successfully in the reaction.³⁹²

Ring expansion may be accomplished by reaction of diazoacetic ester and other similar diazo compounds with cyclic compounds containing unsaturated bonds. Nitrogen is evolved in the reaction and a three carbon ring is established by addition of the carbon atom originally bearing the diazo group at the double bond. A subsequent rearrangement results in the formation of the expanded ring:³⁹³



The reaction has first been studied by *Buchner* and bears his name. Small traces of metals exert a deleterious effect and must be eliminated from the reaction mixture.³⁹⁴

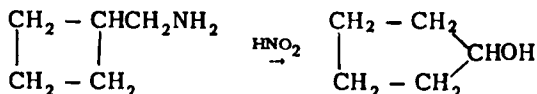
The reaction of benzene with diazoacetic ester proceeds at a good rate in the neighborhood of 130°; it may be carried out successfully at 118° under a positive pressure of 12 cm mercury.

Xylene and mesitylene give some methylated hydrocinnamic esters as by-products by reaction with diazoacetic ester; durene and prehnitine give trimethylhydrocinnamic esters.¹⁰

The reaction has been employed for the preparation of azulenes from hydrindenes.¹¹

Demjanov's Method

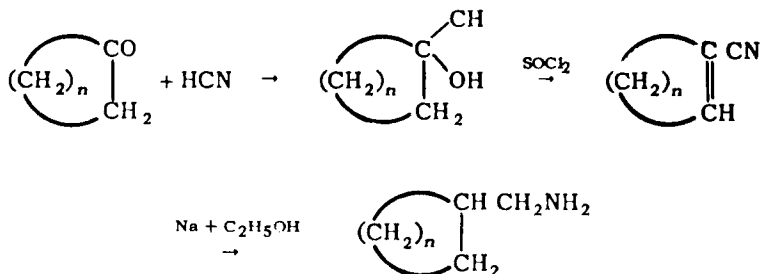
An alicyclic compound bearing an aminomethyl group undergoes ring enlargement when treated with nitrous acid:³⁸²



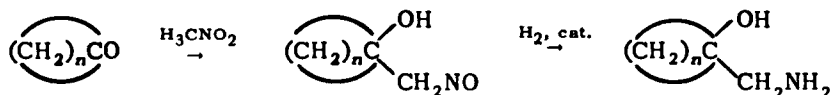
The accepted mechanism of this reaction assumes the initial formation of a diazonium salt, and its breakdown into nitrogen and a carbonium ion, a rearrangement then resulting in ring expansion.

When a methoxy group is attached to a carbon atom in the ring next to that bearing the aminomethyl group, then the entering carbinol group takes a position next to this carbon atom. If a methyl group is attached to a carbon atom removed by at least one carbon atom from that bearing the aminomethyl group, it exerts no directive effect, and both possible isomeric products are formed in equal amounts.³⁹⁷

Oxidation of the resulting carbinol yields a ketone which may again be converted to an aminomethyl derivative, and the process of ring expansion may be repeated. Conversion of the cyclic ketone to an aminomethyl derivative may be accomplished by way of the cyanohydrin, which may be obtained by reaction with hydrocyanic acid in the presence of a trace of a base. The cyanohydrin may be converted to the corresponding aminomethyl compound directly by reduction.³⁹⁸ An alternative method involves the dehydration of the cyanohydrin with thionyl chloride, and reduction of the resulting unsaturated nitrile with sodium and alcohol:



Another route to the amino methyl compound makes use of the reaction of the ketone with nitromethane; reduction of the resulting nitromethyl compound gives the aminomethyl compound.³⁹⁹

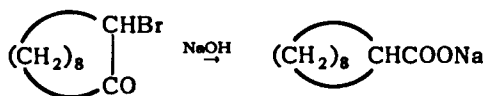


Treatment of the cyclic aminomethyl carbinol with nitrous acid gives the next higher ring ketone.

The transformation of androsterone to *d*-homoandrosterone has been brought about by the application of this method.³⁸³

Ring Contraction

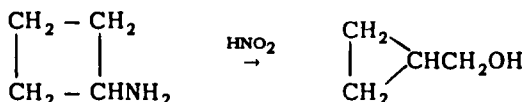
Ring contraction of cyclic ketones has been accomplished by boiling the 2-bromoketone with alkali:⁴⁰⁰



The reaction involves a Faworski transformation. The bromo compound may be prepared by treating the ketone with N-bromosuccinimide.

The dichloride of cyclooctatetraene treated with sodium alcoholate yields a diether which on saponification is converted to an aldehyde of the cycloheptane series.⁴⁰¹

Ring contraction usually takes place when a carbocyclic compound with an amino group attached to a carbon atom in the ring is subjected to the action of nitrous acid.⁴⁰²



Synthesis of Large Ring Compounds

A number of methods of ring closure are applicable to the preparation of large ring compounds. The formation of large ring bodies from metallic salts of long chain dicarboxylic acids has been pointed out previously. Ring formation takes place with varying ease, depending on the chain length. This fact finds its explanation in the *strain theory* advanced by Baeyer.⁴⁰³ This theory is based on the hypothesis of the tetrahedral distribution of valences of carbon postulated by Le Bel and van't Hoff, and rests on two assumptions: first that carbon atoms in an alicyclic ring are unipolar; second, that the valences of carbon, though normally directed toward the apices of a regular tetrahedron, with angles between any valencies equal to $109^\circ, 28'$, they are capable of deviations from these directions. Deviations of the valencies from their normal directions are assumed to create a condition of strain in the ring, which results in a corresponding degree of instability. The greater the deviation involved in the formation of a particular ring, the greater the corresponding strain, and consequently the more difficult the formation of the ring. According to the *rigid group principle*, when the rotational or other movements of atoms in a portion of the chain are prevented by a rigid structure, the probabilities of ring formation are enhanced.⁴⁰⁴

The principle has been utilized in the preparation of cyclooctadiene-(1,5) from glutaraldehyde, which was first converted for the purpose to trimethyl-2,6-dihydroxypiperidine

by reaction with methylamine, reaction with acetonedicarboxylic acid then giving the desired carbon skeleton. Decarboxylation, reduction, and removal of the nitrogen bridge gave the desired compound.⁴⁰⁵ 2,4-Diphenylcyclooctadiene-(1,4) has been synthesized, making use of the same principle, from cyclohexanone by reaction with phenyl styryl ketone. Removal of the carbonyl bridge was accomplished by conversion to oxime and application of the Beckmann rearrangement.⁴⁰⁶ The formation of bicyclic bodies by reaction of nitromalonaldehyde with cyclodecanone and cyclic ketones with more than ten carbon atoms in the ring is an example of the use of the rigid group principle.⁴⁰⁷ The formation of an eighteen carbon ring from the self-condensation of cyclodecane-(1,2) in the presence of sodium ethoxide, is another example of the application of the principle.⁴⁰⁸

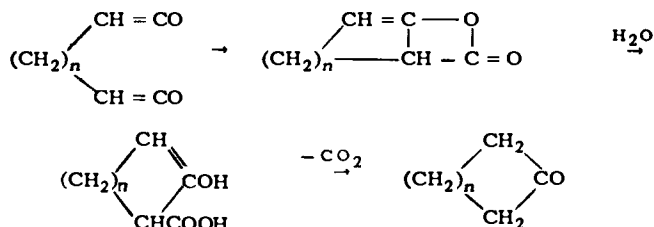
Large ring compounds have been prepared through the cyclization of long chain dinitriles with nitrile groups at the two ends of the chain,⁴⁰⁹ and via the intramolecular acyloin condensation of long chain dicarboxylic esters. Intramolecular aldol condensation, ketene condensation and the intramolecular elimination of sodium halide from halo sodio derivatives are other methods employed for the purpose. In all these methods, the so-called *dilution principle* has been utilized to good advantage. This principle requires the maintenance of a low concentration of the compound to be cyclized, thus reducing to a minimum the coupling reactions involving more than one molecule of the compound.

The subject of *cyclization of dinitriles* has been discussed in Chapter 9 dealing with nitriles. The condensing agent usually employed is the sodium derivative of methylaniline, which may be prepared by causing two atomic equivalents of sodium powder to react with two and one-half molecular equivalents of methylaniline in the presence of one molecular equivalent of styrene.⁴¹⁰ In place of styrene, butadiene, isoprene, or 2,3-dimethylbutadiene may be employed. The condensing agent is sensitive to air and must be protected by a blanket of pure nitrogen.⁴¹¹ Muecon, otherwise β -methylcyclopentadecanone, has been synthesized first by the dinitrile route.⁴¹² The method has been applied to the preparation of large ring oxygen and nitrogen heterocycles.⁴¹³

Potassium *tert*-butylate is a satisfactory agent for internal *acyloin condensation*, which is best carried out in boiling xylene.⁴¹⁴ Seven-membered heterocyclic rings have been obtained in good yield by this method.⁴¹⁵ In this reaction, the terminal groups would appear to be restricted in movement by adsorption on the surface of metallic sodium.⁴¹⁶

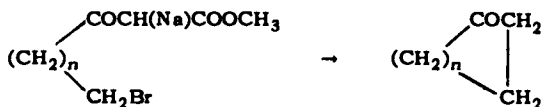
The formation of C_{15} and C_{17} rings has been brought about by intramolecular *aldol condensation*. Acetals of C_{16} and C_{18} dialdehydes were the starting materials. The reaction was carried out in the presence of benzenesulfonic acid and a little water, by refluxing for 21 hours. The cyclic unsaturated aldehydes were obtained in 10 and 30% yield respectively.⁴¹⁷

The dimerization of ω, ω' -diketenes has been used to advantage in the preparation of cyclic ketones:



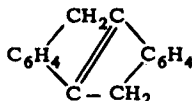
A 33% yield of the seven-carbon ring body, and a 14 to 20% yield of the fifteen-carbon ring have been obtained by this method.⁴¹⁸ The diketenes are obtained from the ω, ω' -dicarboxylic acid chlorides by dehydrochlorination with triethylamine.

The intramolecular elimination of sodium halide from the sodio derivative of ω -haloacylacetic esters has served well for the preparation of large ring compounds:⁴¹⁹

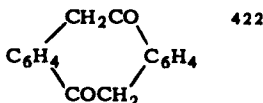


Civetone was first synthesized by this method.

Certain bicyclic systems have been converted to monocyclic systems by oxidative rupture of the bond common to the two rings of the bicyclic system. The classic example is the formation of cyclodecane-1,6-dione by ozonation of $\Delta^{9,10}$ octalin.⁴²⁰ Other examples are the conversion of *cis*-decalin to cyclodecanol-1-one-6 by oxidation followed by treatment with benzoyl chloride in pyridine and hydrolysis,⁴²¹ and the conversion of the compound



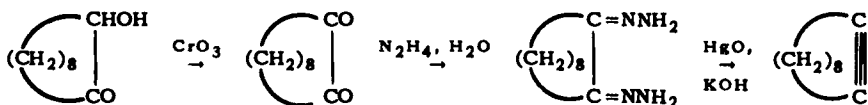
to the eight carbon ring diketone



Some Properties of Macrocyclic Compounds

Amino derivatives of macrocyclic compounds may be converted to macrocyclic *olefinic* bodies by the Hofmann method of exhaustive methylation to a quaternary ammonium compound, and pyrolysis of the free quaternary ammonium hydroxide. Cyclohexyl and cycloheptylamines give exclusively *cis*-cyclohexene and *cis*-cycloheptene. The eight carbon ring amine gives a mixture of the *cis* and *trans* olefins, and compounds with more than eight carbon atoms in the ring apparently yield the *trans* isomer. Certain acids induce the conversion of the *trans* isomer to the *cis* isomer, and since the latter is the more stable form of the eight and nine carbon cyclic olefins, the *cis* isomer may be the principal product in the presence of such acids. In the case of cycloolefins with rings composed of more than nine carbon atoms, an equilibrium condition is established between the *cis* and *trans* isomers.

Cyclic acyloins may be converted to cyclic *acetylenes* by a series of reactions involving oxidation to a diketone, conversion of the latter to a dihydrazone, and finally treatment with mercuric oxide and potassium hydroxide:⁴²³



Cis cycloolefins are unreactive toward phenyl azide, while *trans* isomers are reactive; reactivity increases with increasing ring size up to the nine carbon ring, which may react with explosive violence. Reactivity toward phenyl azide becomes quite low with the ten and eleven carbon *trans* cycloolefins. The middle members of the cycloolefins show reactivity toward hydrazoic acid, diazomethane, etc. They may exhibit dienophile qualities, and may polymerize spontaneously.

1,3-Cyclodienes with five, six, and seven carbon atoms undergo the normal diene addition with maleic anhydride; 1,3-cyclooctadiene fails to undergo diene addition but gives

a mixed polymer instead. Nothing is known about the behavior of the higher cyclic 1,3-diolefins in the diene reaction.

Treatment of cycloolefins of eight, nine and ten carbon rings with peracids yields diols by a process of transannular oxidation, the eight and nine carbon ring compounds giving 1,5-diols, the ten carbon ring bodies yielding 1,6-diols.⁴²⁴ Similar behavior may be expected from olefins having up to thirteen carbon atoms in the ring. Treatment with osmium trioxide and other oxidizing agents results in the formation of the normal 1,2-diols.

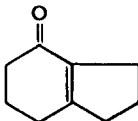
Cycloalkyl bromides in which bromine is attached to a ring carbon atom as well as those with the halogen in a side chain are capable of forming Grignard compounds. Cyclopentyl and cyclohexyl bromide react well, but the higher homologs give the Grignard reagent in low yield. The Grignard compound is obtained in 20% yield from cycloheptane bromide, in 5% yield from cyclooctane and cyclononane bromides, and in 21% from cyclodecane bromide.⁴²⁵

Cyclic ketones with up to seven carbon atoms in the ring readily form bisulfite compounds with sodium bisulfite. Cyclooctanone and higher cyclic ketones fail to react with bisulfite.⁴²⁶ Cyclooctanone reacts with alcoholic bisulfite. Cyclohexanone reacts with hydroxylamine more vigorously than aliphatic ketones; cyclopentanone and cycloheptanone react with the base at a rate comparable with that of aliphatic methyl ketones, while cyclooctanone reacts poorly.

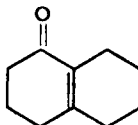
Cyclic ketones undergo the cyanhydrin reaction with hydrocyanic acid in the presence of a small quantity of a base. The equilibrium constants for the reaction, $K \times 10^2$, for the various members from five to eighteen carbon rings ranges as follows: 2, 0.1, 13, 83, 170, 0.0, 112, 31, 26, 6, 11, 9, 12, 10.⁴²⁷

Cyclic keto-2-carboxylic acids with 6, 8 and 10 carbon atoms are enolized to the extent of 40 to 60%; those with 5, 7, 9, 11, 12, 14 and 16 carbon atoms are enolized to the extent of 5 to 15%.⁴²⁸

The middle members of the cyclic saturated hydrocarbons show a tendency toward transannular junction leading to the formation of bicyclic bodies. Cyclooctatetraene almost invariably reacts as a bicyclic compound composed of a fused six and four carbon system. Cyclooctatriene behaves similarly. Dehydrogenation of cyclodecane and cyclodecene gives azulene in 20% yield, together with a 22% yield of naphthalene.⁴²⁹ This appears to be, in effect, the best method for the preparation of azulene. Treatment of cyclononane with N-bromosuccinimide followed by boiling with dimethylaniline results in the formation of $\Delta^{8,9}$ -hyrindone



Similar treatment of cyclodecanone results in the formation of $\Delta^{9,10}$ -octalone-(1)⁴³⁰



Preparation of Long Chain ω, ω' -Bifunctional Compounds

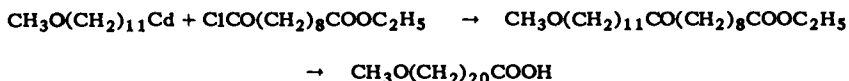
Various methods are available for the preparation of long chain ω, ω' -bifunctional compounds required for the synthesis of macrocyclic bodies.

The Wurtz reaction may be employed for the preparation of ω, ω' -bifunctional paraffins. A satisfactory method is to convert an ω, ω' -diiodoparaffin to an ω -monoaryloxy- ω' -iodo

compound and to subject this to the Wurtz reaction. The resulting diaryloxyparaffin, which possessed twice the chain length of the original diiodo compound, is converted to the corresponding ω, ω' -diiodo body by reaction with hydrogen iodide. Diiodoparaffins with up to twenty and forty carbon atoms have been prepared by this method.⁴³¹

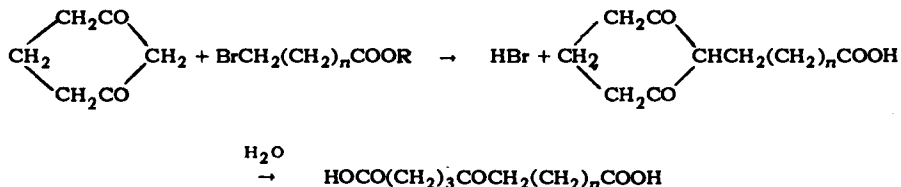
The Kolbe electrosynthesis has also been applied to the synthesis of long chain bifunctional compounds. For this purpose salts of the half esters of ω, ω' -dicarboxylic acids are subjected to electrolysis.

Ketone formation through the reaction of organocadmium compounds with acid chlorides has served as the basis for the synthesis of long chain bifunctional compounds:⁴³²



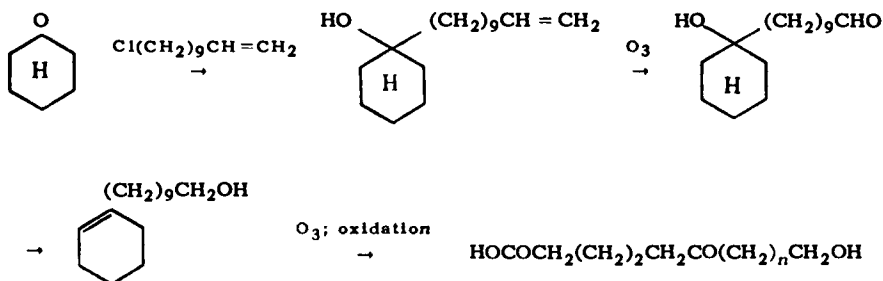
The cadmium compound is prepared through the reaction of cadmium chloride with the corresponding Grignard compound. Yields vary from 10 to 33.7%. The method has been employed for the preparation of all straight chain ω, ω' -dicarboxylic acids with 14 to 22 carbon atoms in the chain.

The reaction of dihydroresorcinol with ω -bromo carboxylic acids in the presence of sodium- or potassium ethoxide gives a derivative, hydrolysis of which results in the formation of a keto ω, ω' -dicarboxylic acid:⁴³³

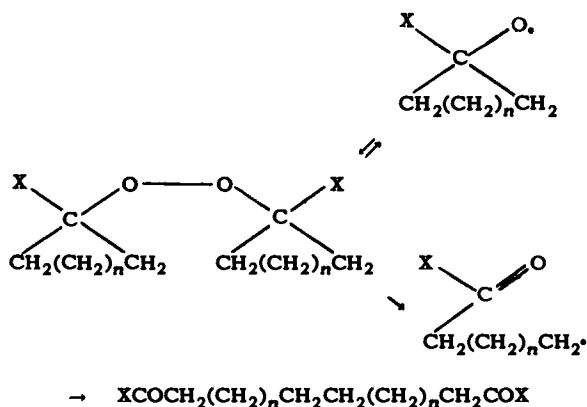


Reduction of the keto group by the Wolff-Kishner method gives the straight chain paraffinic ω, ω' -dicarboxylic acid.

The condensation of the Grignard compound derived from ω -chloro-1,2-ethylenic bodies with cyclohexanone has formed the basis of the synthesis of long chain ω -bifunctional compounds.⁴³⁴ The sequence of steps involved, when the Grignard compound derived from undecylene-10-yl chloride is used in the reaction, are indicated below:

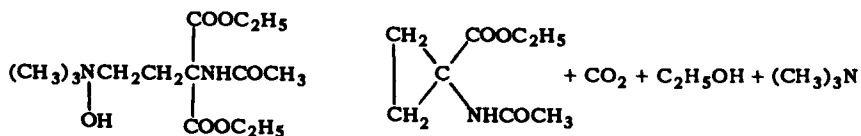


Long chain bifunctional compounds have been prepared from cyclic peroxides by causing their breakdown into radicals, recombination of some of which results in the formation of long chain compounds:⁴³⁵

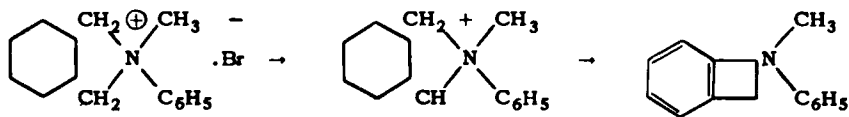


Radical formation appears to be brought about best with ferrous sulfate. It is important to eliminate all atmospheric oxygen from the reaction medium. Yields are usually in the neighborhood of 50%, though yields of 75% have been reported.

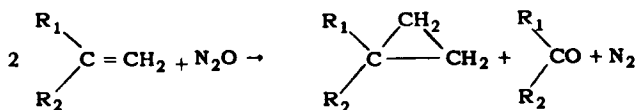
Pyrolysis of certain quaternary ammonium hydroxides, with two carboxy groups attached to the same carbon atom, results in the formation of cyclic compounds:⁵³²



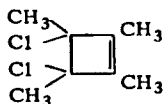
Treatment of methyl phenyl isoindolinium bromide with phenyllithium gives methyl-anilinobenzocyclobutene by a Stevens transformation via an ylid intermediate:⁵³³



1,1-Disubstituted ethylenes react with nitrous oxide giving a cyclopropane derivative:⁵³⁴



Dimethylacetylene treated with sulfuryl chloride gives 1,2,3,4-tetramethyl-3,4-dichlorocyclobutene,⁵³⁵



Hydrogenation of Aromatic Compounds

Saturated cyclic compounds may be prepared through the catalytic hydrogenation of aromatic compounds.

Benzene has been reduced at 180-200° over finely divided nickel.⁴⁸ When benzene is reduced under high pressure at 280° the product is apparently methylcyclopentane.⁴⁹ Hydrogenation at 255° under pressure proceeds rapidly in the presence of nickel oxide; the reaction proceeds less rapidly in the presence of reduced nickel.

The principal product of the hydrogenation of *naphthalene* at 180-200° is tetrahydronaphthalene, but when reduction is effected at 250° and under 120 atm pressure, decahydronaphthalene is obtained. Naphthalene may be readily hydrogenated in the presence of platinum black. If *dihydronaphthalene* is employed as the starting material, two hydrogen atoms are first taken up rapidly, and if hydrogenation is thereafter interrupted, tetrahydronaphthalene is obtained in good yield. When naphthalene is employed as the starting material and the reduction is suspended after four atoms of hydrogen have been absorbed, the product is found to be largely a mixture of decahydronaphthalene and unchanged naphthalene.⁵⁰

The readiness with which phenols are reduced increases with increasing number of hydroxyl groups in the molecule. Resorcinol is easily reduced to cyclohexane-1,3-diol, hydroquinone, pyrogallol and phloroglucinol are also readily reduced, giving cyclohexane-1,4-diol, cyclohexane-1,2,3-triol, and cyclohexane-1,3,5-triol respectively.

Cinnamaldehyde has been reduced to cyclohexylpropyl alcohol at ordinary temperature in the presence of colloidal palladium.

dl-Menthols have been obtained through the catalytic hydrogenation of *thymol* in the presence of platinum catalyst.⁵¹

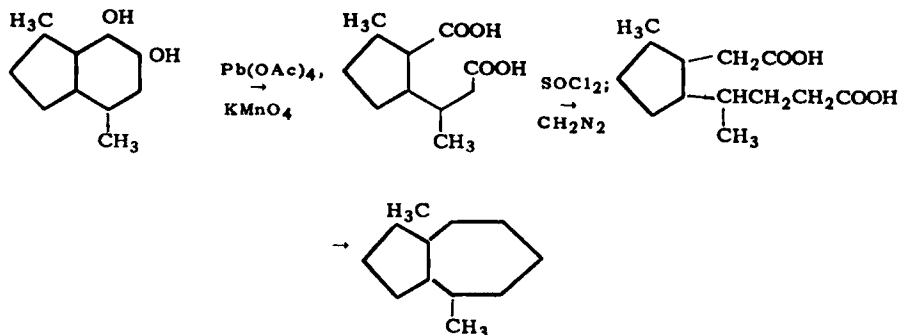
Cyclohexanecarboxylic acid has been obtained in 40 to 50% yield by reducing *benzoic acid* at 300-320° under 200 atm pressure in the presence of nickel oxide. *Phthalic acid* is more readily reduced under the same conditions giving cyclohexane-1,2-dicarboxylic acid. This is probably the best method of preparation of the latter compound. *m-Hydroxybenzoic acid* is reduced to cyclohexanol-3-carboxylic acid; oxidation of this with chromic acid results in the formation of cyclohexanone-3-carboxylic acid. Aromatic esters have been hydrogenated to the corresponding fully hydrogenated alicyclic esters by reduction over platinum or nickel catalyst.²⁶⁸

The reduction of *aniline* in the presence of nickel catalyst at 220-230° under 120 atm gives cyclohexylamine in the comparatively low yield of 40 to 50%, though *diphenylamine* may be converted to dicyclohexylamine in good yield.⁵² *Quinoline* has been successfully reduced to decahydroquinoline.

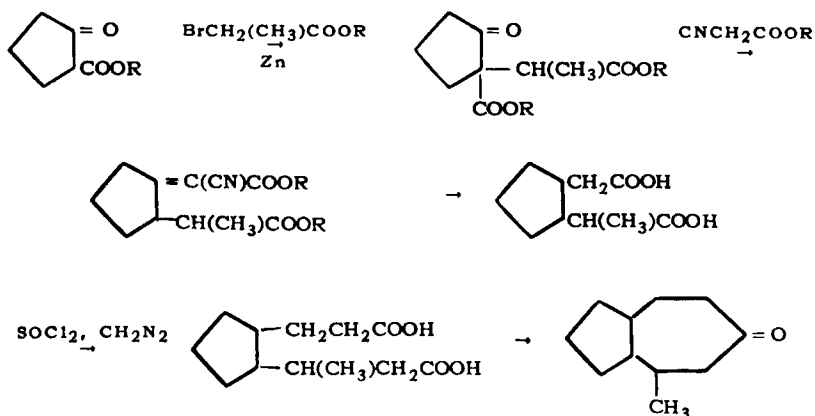
The older method of reduction utilizing *metallic sodium* and *amyl alcohol* has been used successfully for the hydrogenation of *anthranilic acid* to 2-aminocyclohexanecarboxylic acid,⁵³ and of *paraaminobenzoic acid* to 4-aminocyclohexanecarboxylic acid.⁵³ With the former, breakdown of the aromatic ring also takes place, with the formation of some pimelic acid, $\text{HOCO}(\text{CH}_2)_5\text{COOH}$, probably through the intermediate formation of salicylic acid.

Two trans α -decanols have been obtained through the catalytic reduction of α -*naphthol* over nickel. α -*Tetrols* are converted to *cis*- α -decalol on reduction over platinum. *Phenanthrene* is normally converted to the sym-octahydro derivative, but under suitable conditions it may be reduced to the 1,2,3,4-tetrahydro- and 9,10-dihydro derivatives.²⁶⁹ The hydrocarbon has been fully hydrogenated to perhydrophenanthrene over Raney nickel under vigorous conditions.²⁷⁰ The hydrogenation of *anthracene* has been investigated.²⁷¹ Partial hydrogenation leaves one or two rings intact.

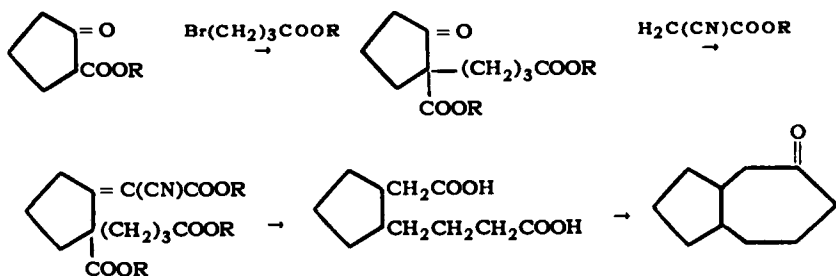
(0,3,5)-decanone-(7) has been prepared starting with veratraldehyde, the aldehyde group of which was first reduced to a methyl group, and the resulting compound was subjected to the Gattermann synthesis. Condensation with malonic ester partial decarboxylation and cyclization gave an indone; this by reaction with methylmagnesium bromide, dehydration and hydrogenation gave 1,4-dimethyl-6,7-dimethoxyindene; hydrolysis of this and oxidation of the resulting 6,7-dihydroxy compound to a methylcyclopentane dicarboxylic acid, followed by application of the Arndt-Eistert synthesis and cyclization gave the desired dicyclocanone.⁴⁴⁷ The last three stages of the synthesis are indicated below:



Cyclopentane derivatives with adjacent carboxyalkyl substituents suitable for the synthesis of the bicyclo structure of azulenes may be prepared from cyclopentanone-1-carboxylic ester by condensation of the appropriate halo ester or nitrile. Condensation with α -bromopropionic ester in the presence of zinc, followed by a Knoevenagel condensation with cyanacetic ester gives a dicarboxylic acid which on reduction, hydrolysis, partial decarboxylation and application of the Arndt-Eistert synthesis yields the required dicarboxylic acid for the synthesis of a bicyclic ketone of the desired type.⁴⁴⁸



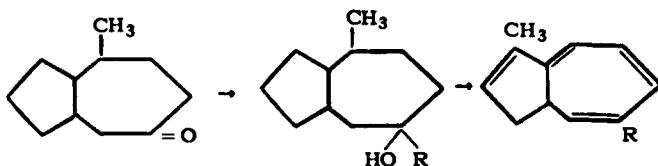
Starting with γ -bromobutyric ester and reducing, hydrolyzing and partially decarboxylating the condensation product with cyanacetic ester, gives a dicarboxylic acid, cyclization of which gives the dicyclic structure with a keto group at 7 position.⁴⁴⁹



The ketone served for the unequivocal synthesis of 7 (or 5) methyl azulene.

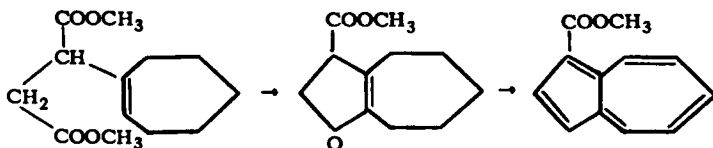
The desired bicyclic structure may be produced starting with cycloheptanone-(1)-carboxylic ester-(2)

In the preparation of a substituted azulene from 2-methylbicyclo-(5,3,0)-decanone by use of alkyl Grignard reagents, a migration of the methyl group to position 1 takes place:⁴⁵⁰

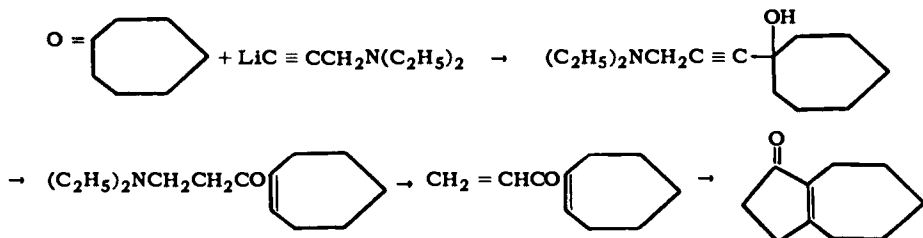


Other similar cases of migration have been observed, demonstrating the uncertainty involved in drawing conclusions regarding the structure of azulenes from the structure of the precursors.

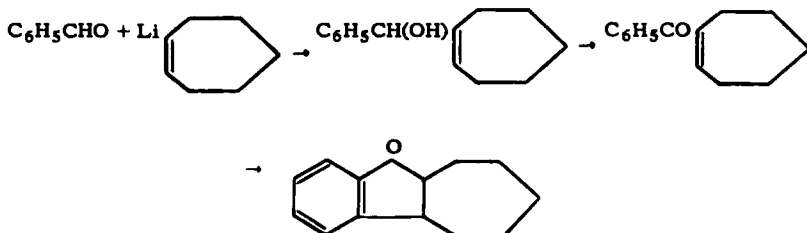
The Stobbe condensation product of cycloheptanone has been utilized for the preparation of azulene-1-carboxylic methyl ester:⁴⁵¹



Condensation of the lithium compound of 3-diethylaminopropin-(1) with cycloheptanone in liquid ammonia, gave 1-(3-diethylaminoprop-1-ynyl)cycloheptan-1-ol, which on heating with phosphoric acid in the presence of a small quantity of mercuric acetate was converted to bicyclo(5:3:0)-dec-1(7)-en-8-one:⁴⁵²

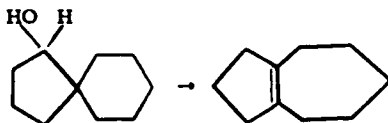


Condensation of benzaldehyde with 1-lithiumcycloheptene gives a phenyl cycloheptene carbinol which, on oxidation to a ketone and cyclization with formic or phosphoric acid, yields a ketoctahydroazulene:⁴⁵³

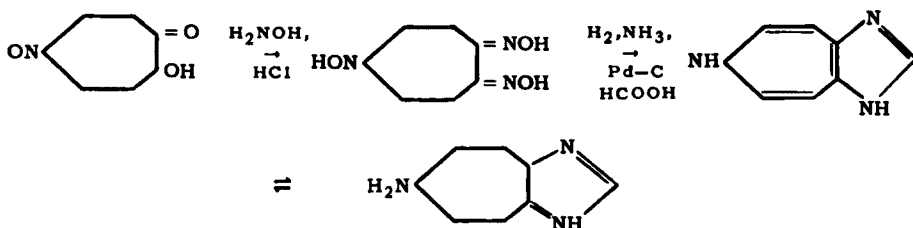


The compound, reduced to an alcohol, dehydrated and dehydrogenated gives benzazulene.

Octahydroazulene has been obtained in 85% yield through a retropinacoline transformation of a spiran, pentamethylene-2,2-cyclopentanone:⁴⁵⁴



1-Azazulenes may be prepared in the form of their hexahydroderivatives from the arylhydrazones of cycloheptanone by the Fischer indole synthesis.⁴⁵⁵ Dehydration with chloranil gives the azazulene generally in 20 to 25% yield. 6-Amino-1,3-diazazulene has been prepared from 5-nitrosotropolone via the dioxime:⁴⁵⁶



Replacement of the amino group by the thiol group and oxidation with nitric acid gives the monosubstituted 1,3-diazazulene.⁴⁵⁷

Azulene hydrocarbons behave in their readiness to undergo substitution more like aromatic phenols than aromatic hydrocarbons.

Chloroazulenes may be obtained by the careful action of chlorine on azulenes.⁴⁵⁸ Unstable monochloro and monobromoazulenes, and crystalline dichloro and chlorobromoazulenes have been obtained by the action of bromo or chlorosuccinimide on azulene.⁴⁵⁹ Nitration of azulenes with nitric acid in an appropriate solvent is possible only when the acid is free of nitrous acid. Nitration of the azulene ring proceeds under milder conditions than that of aromatic bodies. A mononitroazulene has been prepared from azulene by the action of copper nitrate and acetic anhydride.⁴⁶⁰ *Guaiazulene-3-sulfonic acid* has been obtained by the action of the sulfur trioxide-dioxane adduct on guaiazulene.⁴⁶¹

In the azulene ring electron density is especially high on the carbon atoms 1 and 3, and consequently electrophilic or cationoid substituents, in which an atom or group behaves as a cation and a hydrogen atom behaves as a proton, enter preferentially at these positions. Azulenes readily undergo the coupling reaction with even simple diazonium salts at the 1 or 3 positions.⁴⁶² Azulenes give addition products with strong acids such as ferrocyanic acid, 85% phosphoric acid, a fact which has been utilized for their separation. Their picrates, styphnates, tritylates and trinitrobenzoates serve for their identification.

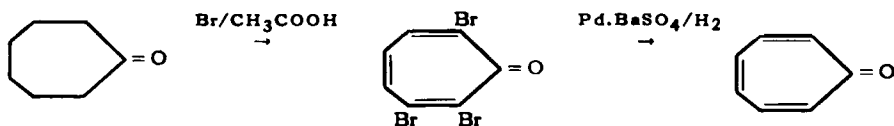
Reduction of azulenes with lithium aluminium hydride often results in the formation of polymeric bodies. 4,8-Dimethylazulene-6-carboxylic acid has been reduced, however, to the corresponding alcohol at -60° by this reagent and the alcohol has been converted to the corresponding aldehyde.⁴⁶³

Dehydrogenation of hydrazulenes by the usual methods, i.e., by use of sulfur, selenium, palladium-charcoal or nickel catalyst, generally results in very low yields of azulenes. Solutions of halogens in nitrobenzene have been employed for the dehydrogenation of small quantities of hydrazulenes; success has often been achieved by this method where other methods failed.⁴⁶⁴ Chloranil has also been employed with success in many instances where other methods of dehydrogenation failed.⁴⁶⁵ Good results are obtained by this method in particular with heptindoles and di- and triazulenes. Tri- and polycyclic azulenes which are formed by the ring expansion method of Buchner by heating to 180 to 200° undergo spontaneous dehydrogenation.⁴⁶⁶

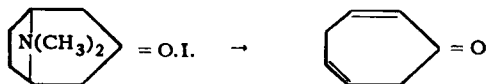
Tropolones⁴⁶⁷

The seven membered ring structure of tropolones may be produced either through the condensation of suberic acid or derivatives of suberic acid,⁴⁶⁸ or by ring enlargement by the Buchner method from cyclohexene or benzene or their derivatives.⁴⁶⁹ The reaction of benzene with diazomethane takes place under the action of ultraviolet rays and gives cycloheptadiene.⁴⁷⁰

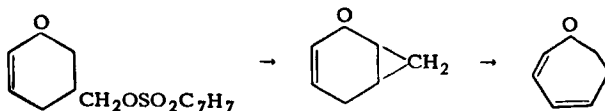
Tropone has been prepared from 2-cyclohepten-1-one by bromination in acetic acid solution followed by hydrogenolysis in the presence of partially poisoned palladium-barium sulfate catalyst:⁴⁷¹



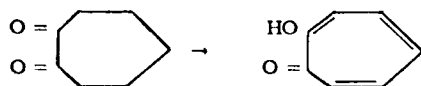
Tropone has also been prepared from cyclohexadienones by reaction with bromine in carbon tetrachloride. Cycloheptadienone has been obtained by the Hofmann degradation of tropinone methiodide:⁴⁷²



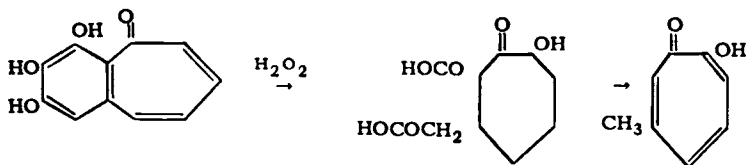
The compound has been prepared also from 3,5-dihydroxybenzoic acid, which was converted to the *p*-toluenesulfonate of 5-hydroxymethylcyclo-2-hexene-1-one which was then converted to cycloheptadienone by treatment with caustic:⁴⁷³



Tropolone has been made by treating 1,2-cycloheptanedione with N-bromosuccinimide in chloroform solution and warming the mixture of brominated products that results for two hours at 90 to 100° .⁴⁷⁴

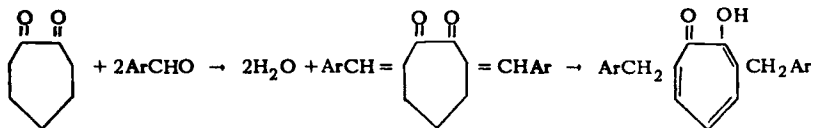


The 5-bromo derivative of tropolone is formed simultaneously in this reaction. Another method of preparation of tropolone makes use of the Buchner ring enlargement of benzene with diazomethane to form cycloheptatriene, which is then oxidized with potassium permanganate to tropolone in 6% yield.⁴⁷⁵ A more satisfactory process utilizes the dimethyl ether of pyrocatechin which, after ring enlargement by the Buchner procedure, is demethylated and oxidized with bromine.⁴⁷⁶ Purpurogallin has been utilized as a starting point for the synthesis of tropolone derivatives; oxidation of this compound with hydrogen peroxide in the presence of caustic results in the formation of a tropolone dicarboxylic acid which may be decarboxylated to 4-methyl tropolone:⁵³⁶



Tropolones undergo various substitution reactions; in their reactivity toward electrophilic reagents they resemble phenols. General preference to 5-substitution is the rule for electrophilic reactions. An important exception is *halogenation* which gives the 3-halo derivatives. A second halogen enters the 7 position and 5-substitution occurs only when 3 and 7 positions are blocked. Bromination of the copper complex of tropolone results in the formation of the 5-bromo derivative.⁴⁷⁷ *Nitration*, which may be effected with a glacial acetic acid solution of nitric acid or with nitrogen tetroxide in light petroleum, yields the 5-nitro derivative as the main product, with smaller amounts of the 3-isomer.³¹¹ Nitro groups present in tropolones facilitate rearrangement of these compounds to the corresponding benzoic acids. Nitrous acid in glacial acetic acid solution converts tropolones to their 5-nitroso derivatives. Fuming sulfuric acid is without action on tropolones at 100-150°, but *sulfonation* may be effected with sulfamic acid. Sulfonation of tropolone gives the 5-sulfonic acid, and possibly some of the 3,5-sulfonic acid.³¹⁰

Tropolones usually fail to undergo substitution reactions in the presence of strong acids.³⁰⁹ Substituents initially enter the 2 position; an exception is diazo coupling, which takes place at 4 position.³¹² The Friedel-Crafts reaction, chloromethylation, and Gattermann's reaction fail to proceed. The presence of tropolone as an anion in basic medium makes nucleophilic substitution in alkaline media much more difficult with tropolone than with the corresponding tropone derivatives. *Diazo coupling* proceeds well in alkaline solution giving the 5-azo derivative, and condensation with alkaline formaldehyde takes place readily. Sandmeyer's reaction proceeds normally with aminotropolones and results in the formation of 4-halo or 4-cyano derivatives.³¹³ Decomposition of the diazonium salts under the conditions that cause the replacement of the diazo group with a hydroxyl group in the benzene series leads to the formation of tropoquinones.³¹⁴ Hydroxy compounds are formed, however, in some instances.³¹⁵ Tropolone undergoes the Reimer-Tiemann reaction to yield the 4-aldehyde.³¹⁶ Aminomethylation may be realized by use of the methylene bis compound of a secondary amine by refluxing in alcoholic solution, but fails under the usual conditions of the *Mannich reaction*. Aromatic aldehydes may be made to condense with 1,2-cyclopentanedione; the product is isomerized by palladized charcoal at 250° to a bisarylmethyl tropolone:



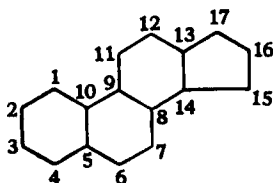
Isomerization may be brought about by heating in a high boiling solvent.

Replacement of the bromine in 3-bromotropolone with a hydroxyl group may be effected by treatment with methanolic sodium methoxide at 140-150°; reaction with potassium hydroxide at 130-140° yields the 4-hydroxy derivative.⁴⁷⁸ The 2-bromine atom in 2,4,7-tribromotropone is most readily replaced with aniline, while in 3,5,7-tribromotropone the 3 and 7 bromines are most readily replaceable.

Oxidation of tropolones with alkaline persulfate yields a mixture of 3- and 5-hydroxy derivatives with the latter predominating.⁴⁷⁹

Sterols 539

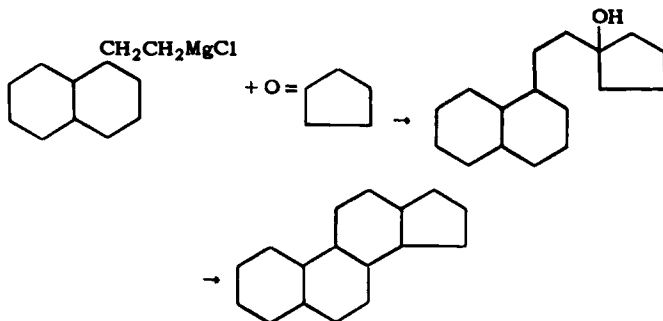
The basic structure of sterols is cyclopentanophenanthrene which is given below with the conventional numbering system:



Methyl groups are combined with the angular 10 and 14 carbon atoms in nearly all natural steroids; the great majority have an OH group at the 3 position. An alkyl chain is often attached at 17 position, and unsaturation appears in many at 5,6-position; in a few at 4,5- or other positions.

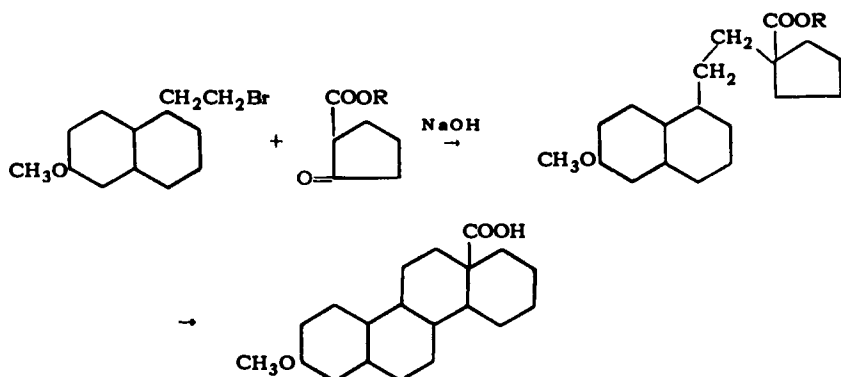
The total synthesis of a compound of the sterol series is generally a highly complex process. It involves the stepwise production of the final complicated tetracyclic structure, with intermediates which make possible the introduction of the various substituents, functional groups and type of bonding at the proper position in the cyclopentanophenanthrene skeleton. The central task is thus often the choice of the appropriate intermediates and of the required methods of cyclization. Numerous methods of cyclization have been employed in these syntheses.

The *Bogert method* has been used in the preparation of cyclopentanophenanthrene, the mother substance of sterols, from cyclopentanone and β -(α -naphthyl)ethylmagnesium chloride:⁵⁴⁰

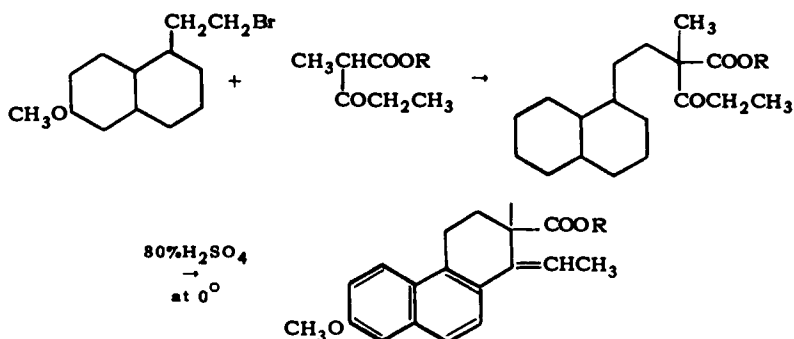


17-Methylcyclopentanophenanthrene was prepared by the same method from β -(α -naphthyl)ethylmagnesium chloride and 2,5-dimethylcyclopentanone.⁵⁴¹ Similarly 3-methoxy-17-methylcyclopentanophenanthrene has been made⁵⁴² from 2-(6-methoxynaphthyl-1)-ethylmagnesium bromide, which may be obtained from Cleave's acid (1-naphthylamino-6-sulfonic acid) through the 1-iodo-6-methoxy derivative.⁵⁴³

The *Bardhan-Sengupta method* has been used in the preparation of cyclopentanophenanthrene derivatives from 1-(β -haloethyl)naphthalenes and 2-carboxycyclopentanones:⁵⁴⁴

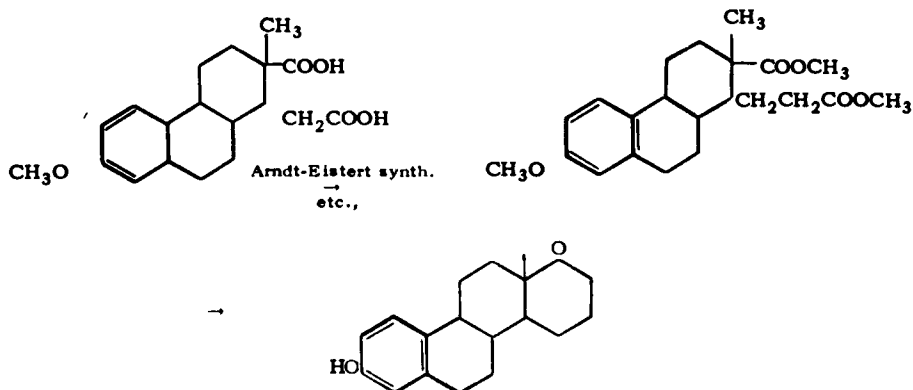


The method is of limited scope because of the difficulty of preparing the required cyclopentanone derivatives. It is well adapted, however, for the production of the phenanthrene ring structure, and has been utilized in the preparation of bisdehydrodoisynolic acid from 6-methoxy-1-(2-bromoethyl)naphthalene, by condensation with α -propionylpropionic acid, followed by cyclization:⁵⁴⁵

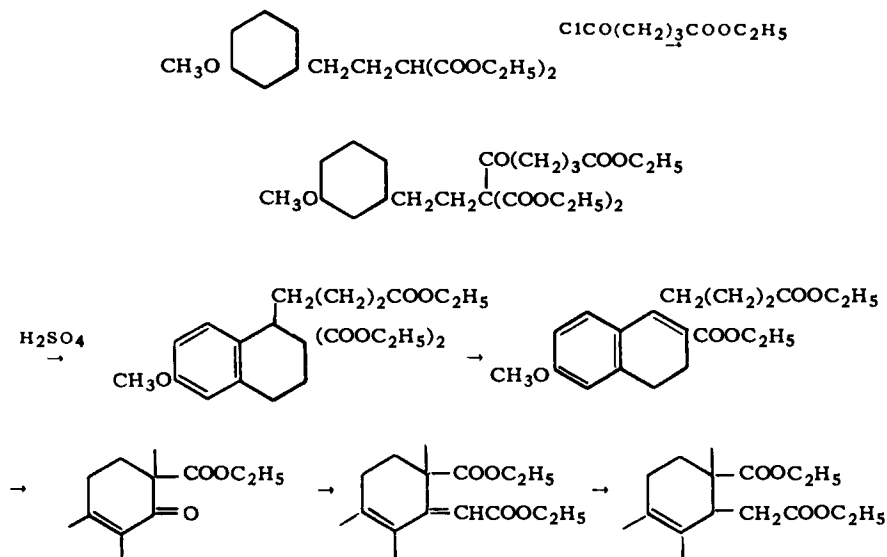


Bisnorbisdehydrodoisynolic acid has been prepared similarly from the same derivative of naphthalene by condensation with acetoacetic ester.

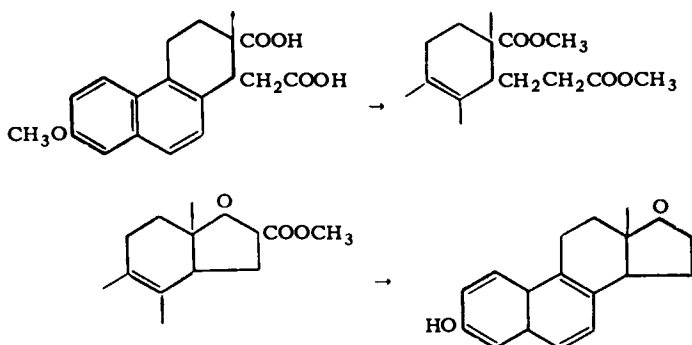
The *Dieckmann condensation* has been employed in several sterol syntheses. It has been utilized in the preparation of estrone from 7-methylhomomarrrianolic ester:⁵⁴⁶



7-Methylhomomarrrianolic ester has been prepared from 1-keto-7-methyloctahydrophenanthrene.⁵⁴⁷ Another synthesis of the ester has been achieved, starting with the condensation product of β -(*m*-methoxyphenyl)ethyl bromide and malonic ester, by the steps indicated below:

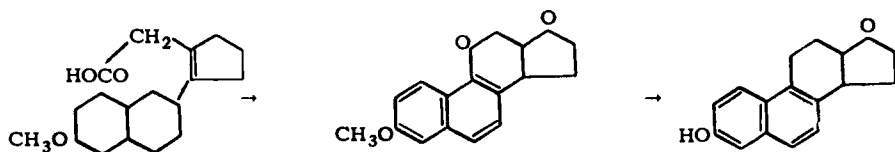


The Dieckmann condensation has played a role in the Bachmann synthesis of equilenin;⁵⁴⁸ the compound was obtained from 7-methylbisdehydromarrrianolic acid by subjecting this to the Arndt-Eistert synthesis and cyclizing the ester of the resulting acid and finally decarboxylating and demethylating the product:

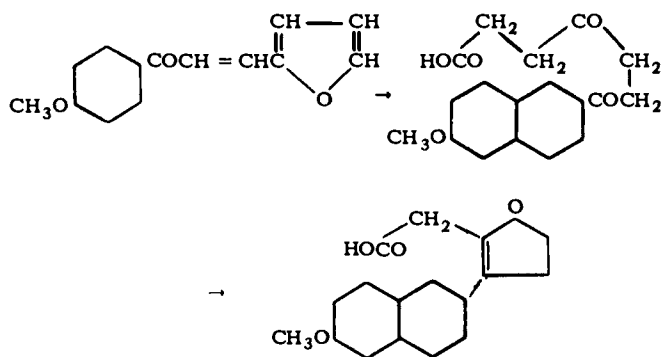


7-Methylbisdehydromarrrianolic acid has been prepared from 7-methoxy-1-keto-2-carboxy-1,2,3,4-tetrahydrophenanthrene⁵⁴⁹ by conventional procedures; the carboxy compound itself was made by condensing 1-keto-1,2,3,4-tetrahydrophenanthrene with oxalic ester and heating the resulting α -keto acid with powdered glass at 180°.

Cyclodehydration of carboxylic acids has been used extensively in the formation of the ring structure of sterols. Norequilenin has been synthesized by the cyclodehydration of 2-carboxy-3-(6-methoxynaphthyl-(2))-cyclopentanone, demethylation, and reduction of the 11-keto group.⁵⁵⁰

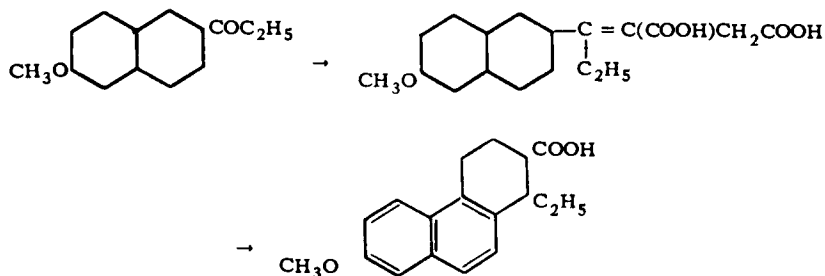


Isoequilenin was prepared from norequilenin by reaction with methyl iodide in the presence of sodamide, after blocking the more reactive 16 position by formylation followed by reaction with methylaniline, the blocking groups being subsequently removed by successive treatment with sulfuric acid and potassium hydroxide. Demethylation with a mixture of hydrogen bromide and acetic acid gave *dl*-isoequilenin. The starting material for the synthesis was the furfurylidene compound resulting from the condensation of 2-acetyl-6-methoxynaphthalene with furfural; hydrolysis of this, and recondensation of the resulting compound gave the desired carboxymethyl compound:



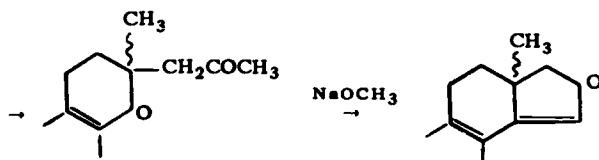
Equilenin methyl ether has been synthesized from the condensation product of 2-methyl-7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene and succinic ester, by partial decarboxylation followed by cyclization.⁵⁵¹

1-Ethyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid has been prepared from the condensation product of 2-methoxy-6-propionynaphthalene and succinic acid by catalytic reduction followed by cyclization with aluminum chloride and a second catalytic reduction:⁵⁵²



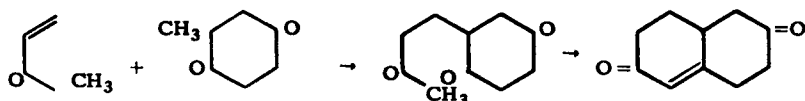
Conversion to *dl*-*cis*-bisdehydrodoisynolic acid methyl ether was accomplished by treatment with diazomethane and methylation with methyl iodide in the presence of sodium triphenylmethane.

3-(6-methoxynaphthyl-1)butyric acid has been cyclized with 90% sulfuric acid to 7-methoxy-1,2,3,4-tetrahydrophenanthrene-1-one:⁵⁵³



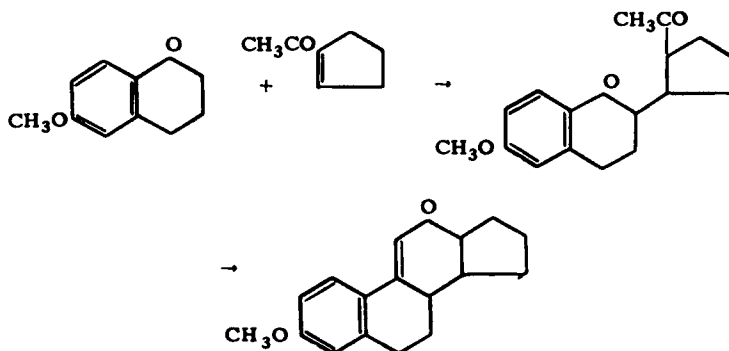
Subsequent steps of carboxylation with methyl carbonate and sodium hydroxide, vigorous hydrogenation, and reoxidation with chromic acid gave an oxoetianate. The monoethylene ketal (I) is obtainable from dihydroresorcinol by two ring expansions and partial hydrogenation.

A diketo methyl octahydronaphthalene has been synthesized from dihydro-2-methyl-resorcinol by condensation with vinyl methyl ketone:³⁶⁷



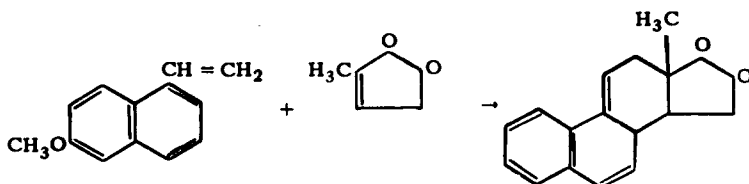
The ring structure of the compound is readily destroyed by hydrolysis, and for this reason considerable difficulties have been experienced in this synthesis. The experimental conditions leading to ring closure were found to be critical. The diketone has been employed in a synthesis of cortisone.

The preparation of a 3-methoxy-12-ketooctahydrocyclopentanophenanthrene has been accomplished from 6-methoxytetralone and α -acetylcyclopentene by a Stobbe condensation followed by a condensation of the methyl group with the carbonyl group in tetralone:⁵⁵⁷



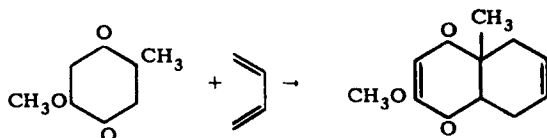
The condensation proceeds best when α -acetylcyclopentene is generated in situ through the decomposition of the appropriate quaternary compound.⁵⁵⁸

The *Diene synthesis* has played a role in a number of syntheses of the sterol ring structure. A 3-methoxy-13-methyl-16,17-diketoheptahydrocyclopentanophenanthrene has been made through the condensation of 1-vinyl-6-methoxynaphthalene with methylcyclopentenedione:⁵⁵⁹

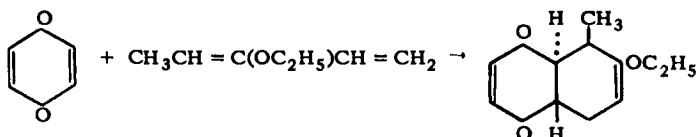


This adduct has been converted to an stereoisomer of estrone. Condensation of the vinylmethoxynaphthalene with cyclopentenone gives an isomer of dehydronorequilenin.

An intermediate which has served in the Woodward synthesis of cortisone³⁶⁸ has been prepared through the condensation of 2-methyl-5-methoxybenzoquinone with butadiene:

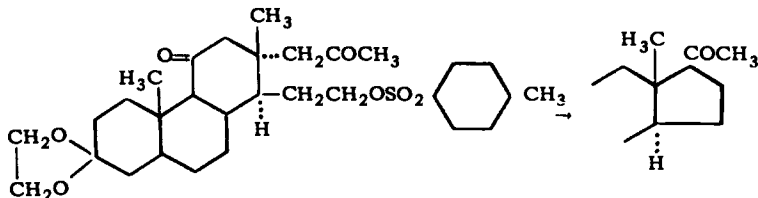


A diene condensation of benzoquinone with 3-ethoxypenta-1,3-dione gives a product which served as an intermediate in the Sarett synthesis of cortisone:³²⁸

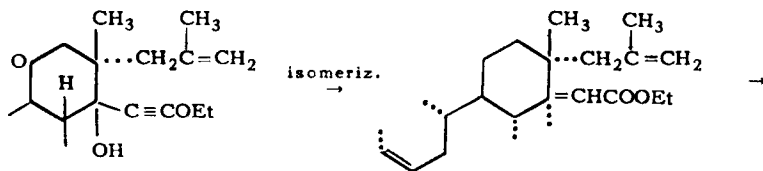
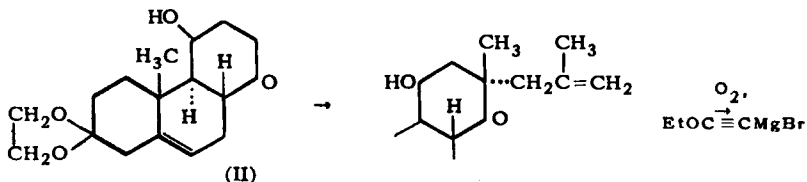


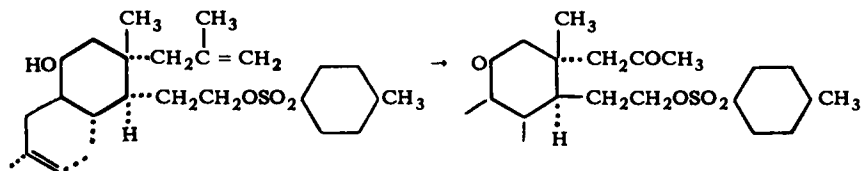
This adduct, though stereochemically unstable, was successfully reduced in benzene solution with Raney nickel to a saturated dihydroxyketone without isomerization.

Cyclization to a five carbon ring has been brought about by internal condensation of the toluenesulfonyl ester of a keto hydroxyethyl compound in the presence of sodium methoxide in Sarett's stereospecific synthesis of cortisone

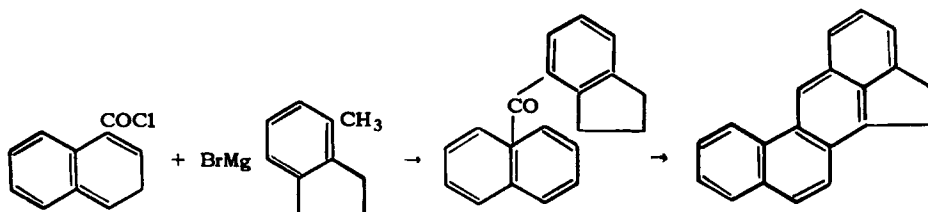


The sulfonyl ester was prepared from the hydroxydiketo monoacetal (II) by a succession of steps involving methylation and methallylation, oxidation and condensation with ethoxyacetylenemagnesium bromide, followed by isomerization, hydrolysis, a series of reductions, esterification with the sulfonyl chloride and oxidation:





*Elbs condensation*⁵⁶⁰ has been employed in the synthesis of methylcholanthrene:⁵⁶¹

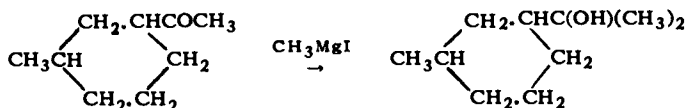


Methods Employed for Modifying Compounds without Ring Closure or Fissure

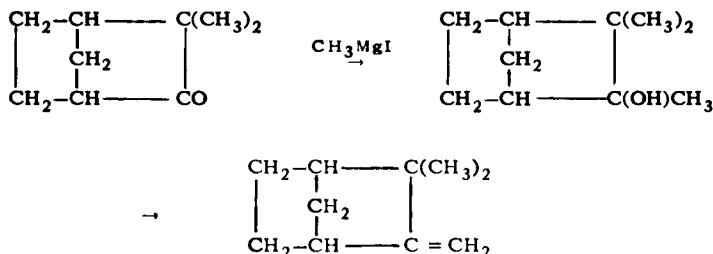
Numerous general methods have been employed for the purpose of bringing about modifications in a cyclic compound without affecting the ring itself. These methods depend upon the presence of a reactive group, such as a carbonyl or carbinol group, an unsaturated linkage, or a reactive methylene, in the molecule of the compound.

The *Grignard reaction* may be utilized for the introduction of alkyl or other groups into the molecules of ketones or aldehydes by reaction of a Grignard reagent with the carbonyl group.

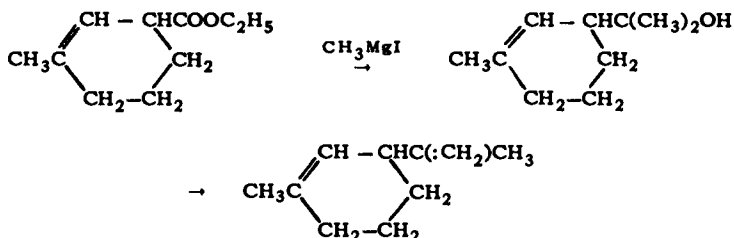
An example is afforded by the preparation of d-dihydrosylvoterpineol from d,1-methylcyclohexane-3 methyl ketone and methylmagnesium iodide:⁵⁴



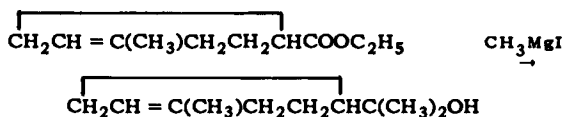
The preparation of methylcyclohexanol-3-carboxylic acid from cyclohexanone-3-carboxylic acid, and of camphene from camphenilone present other examples. Camphene is prepared from the alcohol first obtained by dehydration:



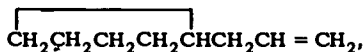
Carvestrene has been prepared by the dehydration of the alcohol obtained from methylmagnesium iodide and 1-methylcyclohexene-5-carboxylic ethyl ester:⁵⁵



Another example of the use of an ester is the preparation of *dl*- α -terpineol from 1-methylcyclohexene-4-carboxylic ester and methyl magnesium iodide:²⁸

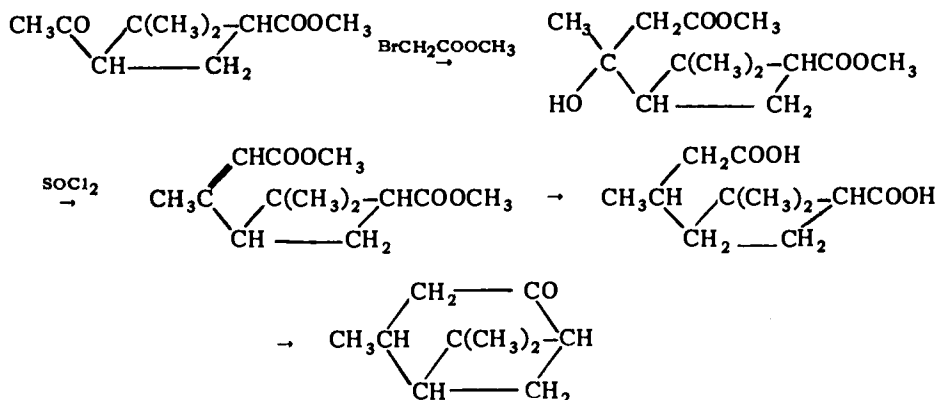


A Wurtz type reaction making use of Grignard reagents may be utilized for the introduction of organic groups into ring compounds. Allylcyclopentane,

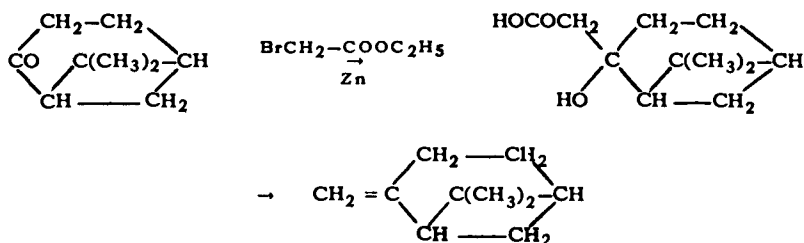


has been obtained, for example, from cyclopentylmagnesium bromide and allyl bromide.²⁶³

Reformatsky's reaction is utilized in the preparation of certain terpenes. Thus, the condensation product of methyl pinonate and methyl bromoacetate has been used as an intermediate in the synthesis of *dl*-verbanone, the ester being dehydrated and finally hydrogenated and cyclized for the purpose:⁵⁶



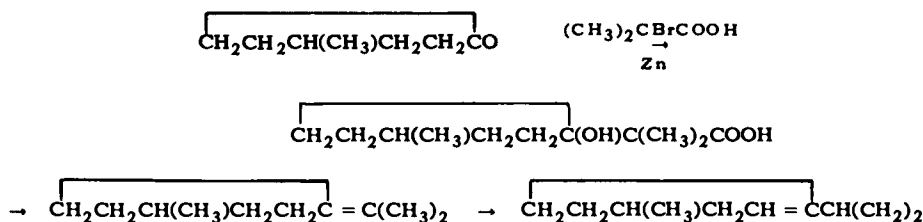
A partial synthesis of β -pinene has been effected through the condensation of nopione and ethyl bromoacetate in the presence of zinc, the resulting acid being subsequently purified and dehydrated and decarboxylated with sodium acid sulfate to *l*- β -pinene:⁵⁷



Distillation of the crude acid under diminished pressure gave mainly *l*- α -fenchene.

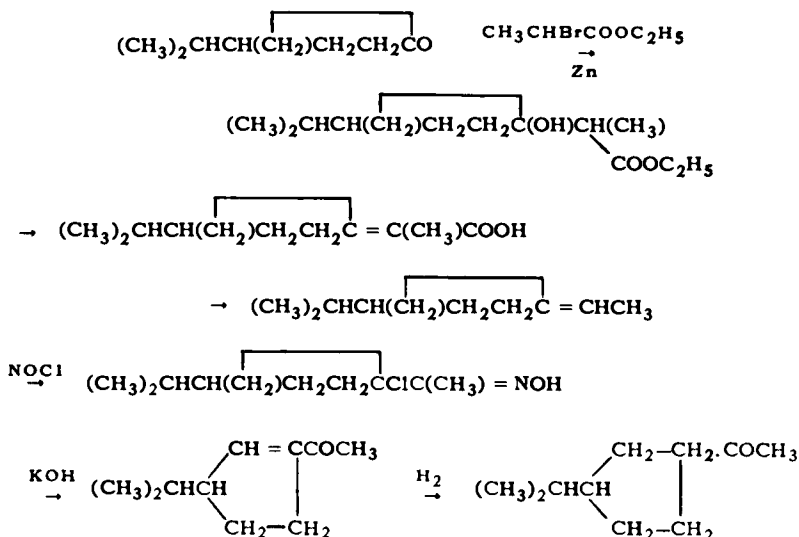
The reaction product of α -bromopropionic acid with 1-methylcyclohexane-4-one has been employed as the starting point for the synthesis of $\Delta^{3,8}$ -*p*-menthadiene.⁵⁸

Menthene has been synthesized from the reaction product of 1-methylcyclohexane-4-one and α -bromoisopropionic acid by dehydration and decarboxylation, the resulting unsaturated compound being finally isomerized:⁵⁹



The reaction product of *dl*-methylcyclohexane-3-one and α -bromopropionic ester has been employed in the synthesis of dihydrosylvesterpineol.⁵⁴

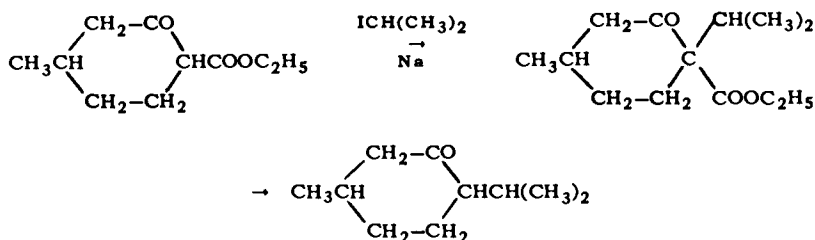
Isopropylcyclopentan-3-one and α -bromopropyl ester reacting in the presence of zinc give a hydroxy ester which has been employed in the synthesis of dihydropinalone. The steps involved are dehydration and decarboxylation, followed by reaction with nitrosyl chloride, then with potassium hydroxide, and finally hydrogenation of the unsaturated bond in the ring:



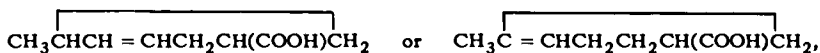
Camphenic acid, $\text{CH}_2\text{CH}_2\text{CH}(\text{COOH})\text{CH}_2\text{CH}(\text{CH}_3)_2\text{COOH}$, has been synthesized from cyclopentanone-3-carboxylic ester and α -bromoisobutyric ester by dehydrogenating the resulting hydroxy dicarboxylic ester and subsequently reducing the unsaturated acid obtained.⁵⁹

Alkylation of terpenes containing a carbonyl group in the ring by use of sodium, sodium ethoxide, or sodium amide and an alkyl iodide proceeds successfully as a rule. Thus, ethyl iodide and sodium amide reacting with menthone give 2-ethyl-*p*-mentanone-(3). Mono and dialkylated derivatives of camphor have been prepared by this method from camphor.⁶⁰

Menthone has been synthesized from ethyl β -methylpimelate by treating its sodium derivative with isopropyl iodide and decarboxylating the resulting compound:⁶¹

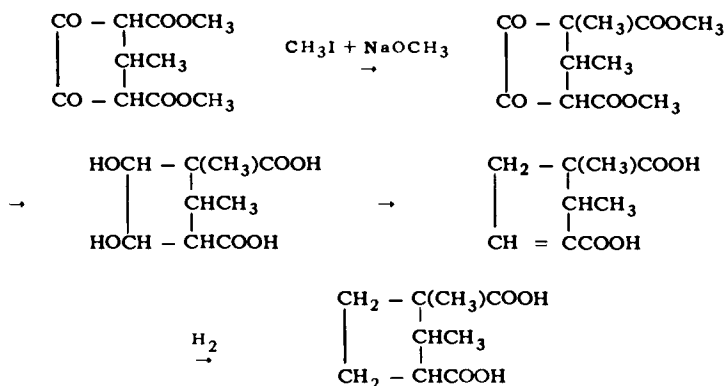


1-Methylcyclohexan-6-one-3-carboxylic acid has been obtained from the sodium derivative of ethyl cyclohexanone-2,4-dicarboxylate and methyl iodide. 1-Methylcyclohexan-3-carboxylic acid,

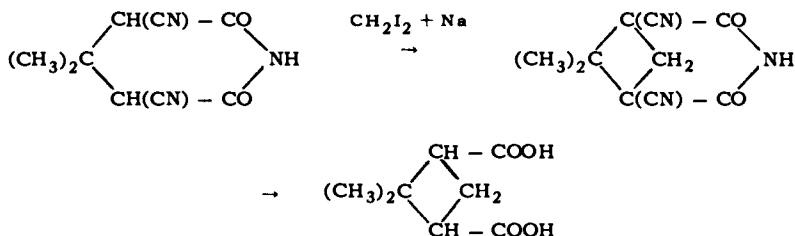


has been prepared from this acid by partial decarboxylation, reduction to an alcohol and dehydration.⁶²

cis-Allosantenic acid has been prepared from the condensation product of oxalic acid and dimethyl β -methylglutarate, by methylation with methyl iodide and sodium methoxide, followed by reduction with sodium amalgam, then with phosphorus and hydriodic acid, the resulting unsaturated dicarboxylic acid being then hydrogenated over platinum catalyst:¹⁵



Norpinic acid has been obtained from the cyclic dimethyldicyanoglutarimide by reaction with sodium and methylene diiodide and subsequent hydrolysis and partial decarboxylation:⁶³

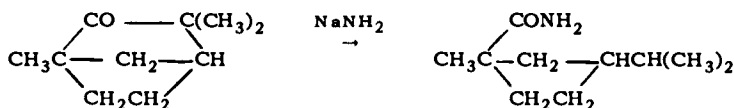


The carboxyl group may be introduced in certain terpenes having a reactive methylene group through the action of sodium amide and carbon dioxide.

Verbanone has been carboxylated by this method,⁶⁴ and the resulting acid has served as the starting point for the synthesis of pinocamphone. The steps involved are reduction of the carbonyl group to carbinol, dehydration, and finally treatment of the chloride of the unsaturated acid with sodium azide and application of the Curtius reaction to obtain the saturated ketone.

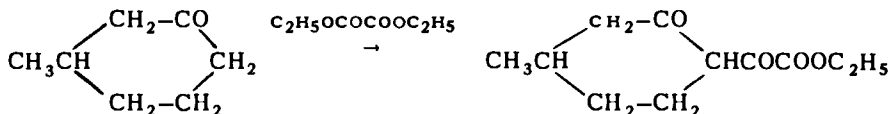
The sodio derivative of santenone gives, on treatment with carbon dioxide, santenone-carboxylic acid.⁶⁵

Fenchone digested with sodamide in benzene solution undergoes ring fissure giving d-fencholamide:



Camphene is similarly cleaved on treatment with sodamide in benzene solution.⁶⁶

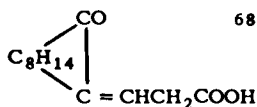
Ester condensation is possible, involving a reactive methylene group in terpenes. Thus, *d*-3-methylcyclohexanone has been condensed with ethyl oxalate yielding a diketo acid:⁶⁷



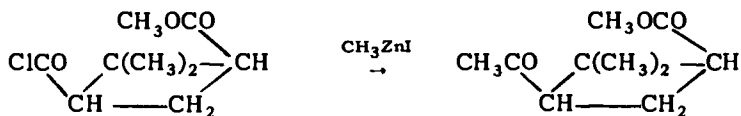
This acid has served as the starting point for a synthesis of menthone.

Camphor reacts with relative ease with sodium or sodium amide to form camphor sodium. This compound has served for the preparation of various derivatives of camphor.⁶⁸ Hydroxymethylenecamphor has been obtained through the reaction of amyl formate with camphor sodium.⁶⁹ Hydroxymethyleneisofenchone is similarly obtained from isofenchone by the action of sodium and amyl formate.⁷⁰

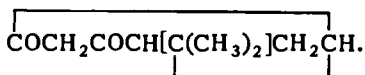
Hydroxymethylenecamphor condenses with malonic acid in the presence of pyridine to give an unsaturated acid,



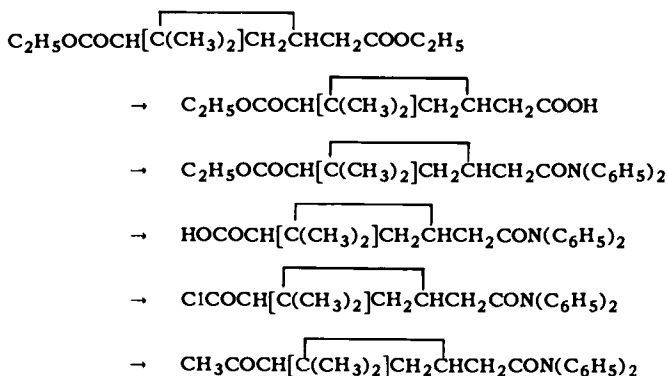
The *keto* group may be formed in cyclic hydrocarbons containing carboxyl groups through the reaction of the chloride of the acid with a zinc alkyl chloride or a cadmium alkyl chloride. An example is offered by the synthesis of pinonic acid from norpinic acid chloride:⁷¹



The ester is readily cyclized under the action of metallic sodium to ketonorpinone,



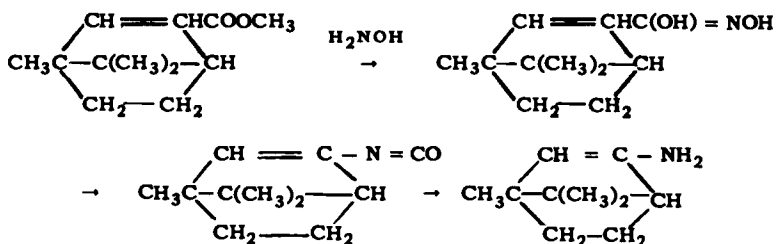
In the preparation of pinonic acid from pinic acid by this method, it is important to protect one carboxyl group. This has been accomplished successfully by the partial hydrolysis of the neutral ester, and conversion of the acid ester obtained to diphenylamide ester over the chloride. Hydrolysis of the amide ester gives the desired free acid, which is then converted to the ketone via the chloride:⁷²



The amide group may be removed by heating with alcoholic alkali to form *dl-trans*-pinonic acid.

The *Lossen rearrangement* may be made use of for the replacement of carboxyl groups with amino groups, the isocyanate formed being hydrolyzed to the amine.

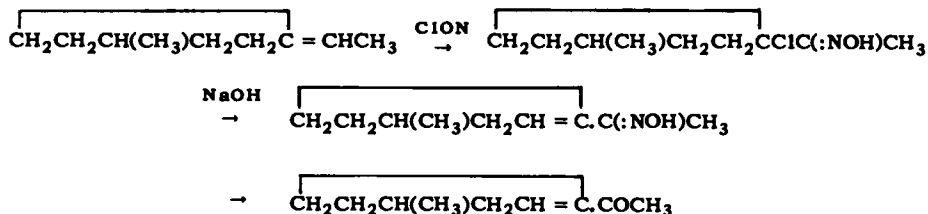
This transformation has been applied to methyl *d*-bornylene-3-carboxylate which, on reaction with hydroxylamine in the presence of sodium methoxide, gives the corresponding hydroxamic acid:⁷³



The amine in this instance isomerizes to the imine, which is hydrolyzed to *epicamphor*.⁷⁴

The formation of a ketonic group at an unsaturated carbon atom may be brought about through nitrosochlorination followed by dehydrochlorination and hydrolysis.

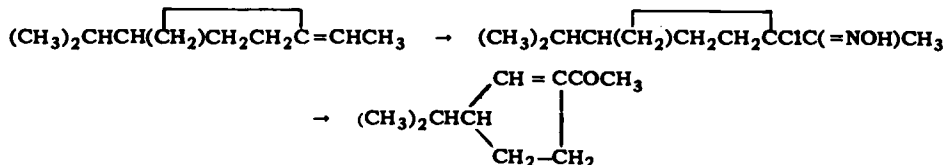
This method has been employed for the preparation of $\Delta^3,8$ -menthadiene from 1-methylcycloheptene-4-one after condensation with α -bromopropionic ester by Reformatsky's reaction and dehydration of the resulting alcohol:⁵⁸



Treatment of the unsaturated ketone with methylmagnesium iodide, hydrolysis, and dehydration of the alcohol obtained results in the formation of the menthadiene,

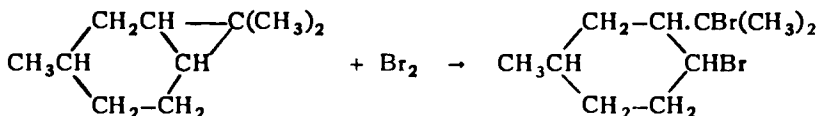


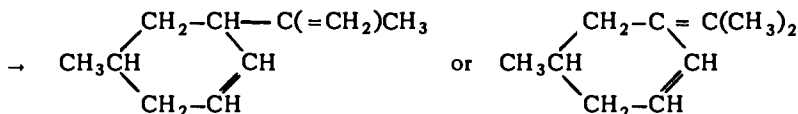
Another example of the use of the method is afforded by the preparation of *dihydropinone* from the condensation product of isopropylcyclopentane-3-one and ethyl α -bromopropionate by Reformatsky's method, the unsaturated compound obtained by the dehydration of the resulting alcohol being subjected to the treatment described:



Reduction of the unsaturated ketone gives dihydropinolone,

Dehydration or dehydrohalogenation are the usual methods employed for the formation of unsaturated bonds in a molecule. *m*-Menthene has been prepared, for example, by brominating *d*-carene and heating the dibromide with quinoline

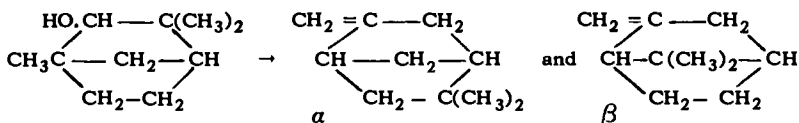




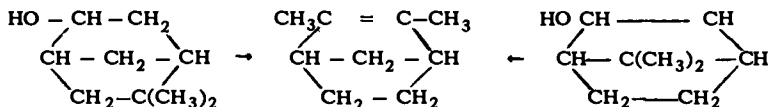
Δ^3 -*p*-Menthene is obtained in over 90% yield by the action of 1-2% sulfuric acid on 1-menthol.⁷⁵ Dehydration of the isomeric menthols does not proceed with equal ease.

Terpineol, $(\text{CH}_3)_2\text{C(OH)CHCH}_2\text{CH}=\text{C(CH}_3\text{)CH}_2\text{CH}_2$, results on treating terpin, $(\text{CH}_3)_2\text{C(OH)CHCH}_2\text{CH}_2\text{C(OH)(CH}_3\text{)CH}_2\text{CH}_2$, with very weak dehydrating agents.⁷⁶

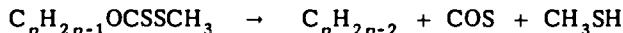
Direct dehydration of the alcohol may result in molecular rearrangements in the terpene series. Thus, when fenchyl alcohol is dehydrated, intermolecular migrations take place, and α - and β -fenchenes are formed:



Ozonolysis of these compounds leads to the formation of α - and β -fenchocamphorones which, upon reduction to the corresponding alcohol, followed by dehydration give santene,⁷⁷ the formation of the latter involving a Wagner or Nametkin rearrangement:



Tchugaev has originated a method which makes possible the formation of a double bond in terpenes under mild conditions.⁷⁸ The alkali metal derivative of a terpene alcohol is converted into the xanthate by reaction with carbon disulfide; the xanthate is converted to methyl xanthate and this is distilled under atmospheric pressure to give the unsaturated compound, together with carbon sulfoxide and methyl mercaptan:



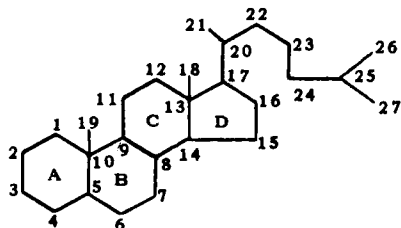
Isomerization is avoided under the conditions of the reaction, and the method is suitable for the dehydration of alcohols of the terpene series. Thujyl alcohol, for example, has been dehydrated by this method.⁷⁹

Another method which renders possible the formation of unsaturated bonds in terpenes without inducing isomerization consists in fully methylating the amino derivative, converting the methylated amine to the quaternary compound, and distilling the free ammonium compound under diminished pressure. Pinene has been prepared by this method from pinocamphylamine.

Modifications in the Molecule of Steroids without Change in the Ring Structure²⁷²

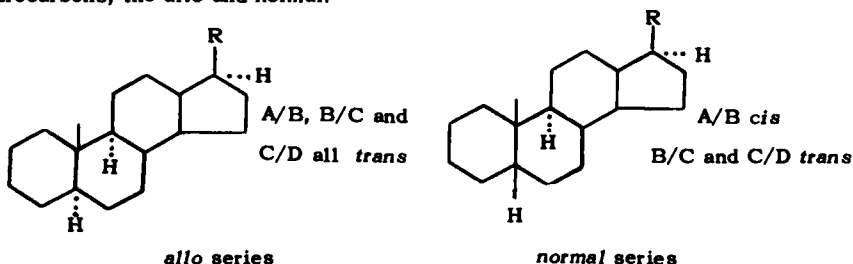
Methods of modification of the structure of steroids without change in the ring skeleton have played an important part in the synthesis of the various individual compounds of this class. Modification is dependent upon the presence of a group capable of undergo-

ing chemical change. The carbon skeleton of cholesterol, typical representative of this class of compounds, is given below with the accepted numbering system to serve as reference for the descriptions that are to follow.



The position of an atom or group lying above the general plane of the ring system is designated by the Greek letter β , that of one lying below this plane by the letter α . The former position is represented by a full line, the latter by a broken line. An unknown position is designated by ζ and is represented by a wavy line. A compound with a hydrogen of α orientation at C 5 is designated by the prefix *allo*. A substance differing from a typical natural steroid in respect to the orientation of a hydroxyl group is termed an *epi* compound. For distinction of configuration of C 20 and C 24 the suffixes *a* and *b* or the designation *n*- and *iso* are employed. These serve to distinguish stereoisomerides without any spatial implication, and designations applied provisionally in one series imply no correspondence to those in another.⁴⁸⁰

There are seven asymmetric centers in the nucleus at positions 5, 8, 9, 10, 13, 14 and 17, making possible 128 stereoisomerides. Fusion of the rings A and B may be either *trans* or *cis*, with other rings in *trans* junction giving two possible series of isomeric hydrocarbons, the *allo* and *normal*:



Modifications Involving the Hydroxyl Group

Hydroxyl groups in the molecule may be oxidized to carbonyl groups, or if present at the end of a chain, in stages, to carbonyl and carboxyl groups. Oxidation may be accomplished by use of chromium trioxide in acetic acid. Oxidation may be a selective process, as in the case of cholestantriol in which the hydroxyl groups at 4 and 7 position are converted to carbonyl groups but one at position 6 is left intact.²⁷³ A hydroxyl group at position 6 is, in general, more readily attacked than one at 3. Selective oxidation is possible by partial blocking. *Testosterone* has been prepared from androstene-3,17-diol by converting the 3-monoacetate to the 3-monoaceto-7-benzoate, partially hydrolyzing this to the 7-benzoate, oxidizing the monobenzoate by the Oppenauer method and finally hydrolyzing the resulting benzoate of the 3-keto-7-alcohol with acid. The selective oxidation of the 1-hydroxyl in a 1,7-dihydroxyphenanthrene derivative has been effected by blocking the 7-hydroxyl group with the trityl group. Allylic type alcohols may be oxidized to the corresponding ketones by manganese dioxide.⁴⁸¹

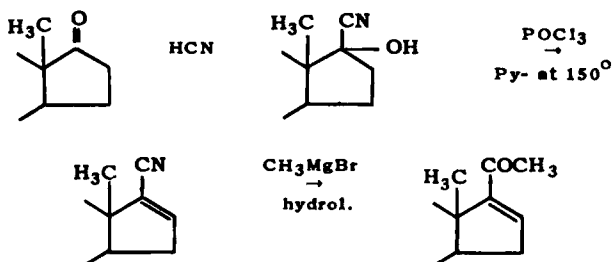
The hydroxyl group may serve the purpose of introducing *ethylenic bonds* in the sterol molecule. This may be accomplished in various ways. Use of a dehydrating agent is one possible method; pyrolysis of acetic or benzoic esters is another possible route.²⁷⁴

Replacement of the hydroxyl group by a halogen and subsequent dehydrohalogenation also brings about the desired result.

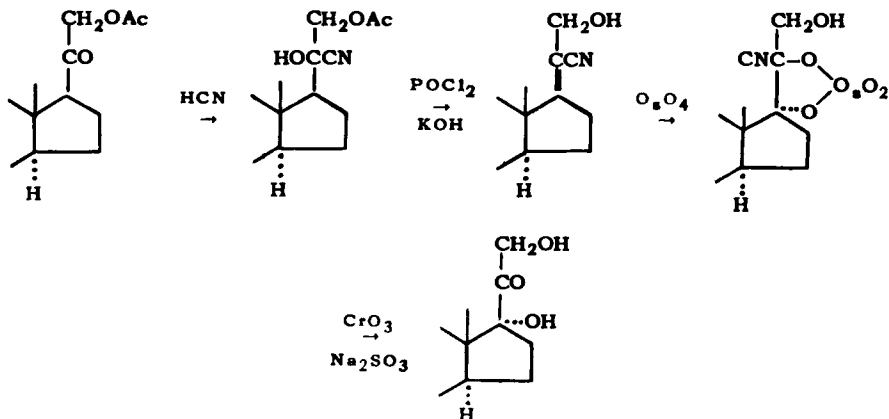
The carbethoxylation or catylation of steroid hydroxyl groups by ethyl chloroformate is a selective process. Esters $\text{ROCOOC}_2\text{H}_5$ are formed preferentially from "equatorial" hydroxyl groups. Thus, of the three hydroxyl groups in methyl cholate only one, the equatorial 3α , reacts even when an excess of the reagent is available.²⁷⁵

Modifications Involving Carbonyl Groups

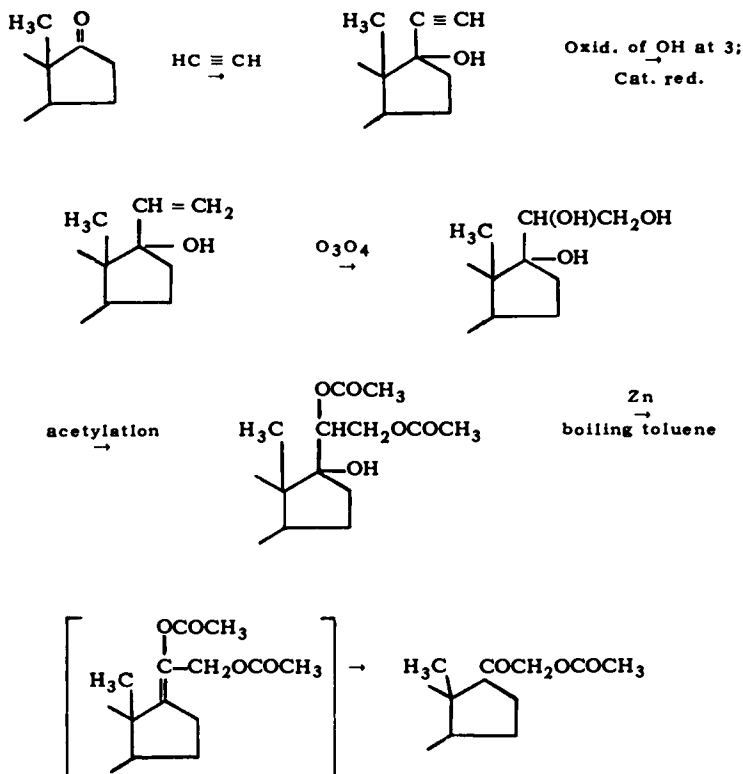
A carbonyl group present in the molecule of a sterol makes possible many modifications. Organic groups may be attached to the carbonyl carbon by means of the Reformatsky reaction or the Grignard reaction. The resulting hydroxy compound may be subjected to further changes; more specifically, it may be converted to an unsaturated compound. Carbonyl compounds may be converted to cyanohydrins by reaction with hydrocyanic acid in the presence of a trace of base. The cyanohydrin may be converted to an unsaturated nitrile by dehydration. The cyano group may be subjected to various changes; in particular it may be converted to a keto group by the Grignard reaction. The keto group in dehydroepiandrosterone has been converted to a hydroxy cyano group, then to an unsaturated nitrile by treatment of the cyanohydrin with phosphorus oxychloride followed by heating at 150° with pyridine. The unsaturated nitrile was converted to a methyl ketone by reaction with methylmagnesium bromide and subsequent hydrolysis:²⁷⁶



Pregnenolone and progesterone have been prepared from the unsaturated keto body by further transformations. The carbonyl group in 20 position in 3α -21-diacetoxypregnane-1,20-dione has been converted to cyanohydrins, dehydrated to the 17,20-olefinic nitrile and the acetylated product oxidized by osmium tetroxide to obtain the 17-hydroxy-20-carbonyl compound.⁴⁸²

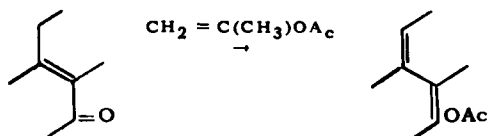


The acetylenic group may be introduced at a carbonyl group by reaction with dipotassium acetylide in liquid ammonia. Serini's synthesis²⁷⁷ of desoxycorticosterone acetate from dehydroepiandrosterone involved this condensation as the first step. This, and the subsequent steps in the synthesis are indicated below:



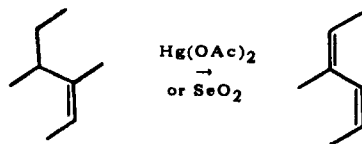
The second step indicated, e.i. oxidation of the 3-hydroxyl group to a keto group, was carried out by the Oppenauer method. A remarkable steric change is involved in the last step in this series of reactions, a side chain at position 17 undergoing a shift in position from β to α .

The tendency of the keto group to enolize makes possible the introduction of an ethylenic linkage in the molecule. $\Delta^{8(9)}$ -7-Ketones have been converted to monoenoil acetates by reaction with isopropylidene acetate:²⁷⁸

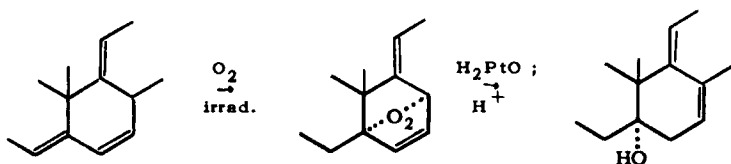


Pregnane-2:1:20-trione gives a dienol triacetate with a mixture of acetic anhydride and *p*-toluenesulfonic acid.²⁷⁹

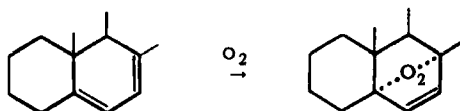
A 7:8, 9:11 diene system may be established in various ways. Starting with a steroid having a 7:8 olefinic bond, oxidation with mercuric acetate⁴⁸³ or with selenium dioxide⁴⁸⁴ will accomplish the purpose:



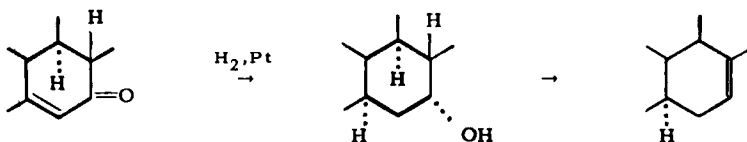
A 7:8, 9:11 diene system has been established in dehydroergosterol by an interesting series of transformations. This sterol possesses ethylenic linkages at 9:11, 4:5 and 6:7 positions. Oxygen irradiation eliminated the 4:5 ethylenic bond, establishing a 5 α =8 α epidioxide bridge; careful catalytic hydrogenation with platinum oxide and subsequent treatment with acid established the 7:8, 9:11 diene system:



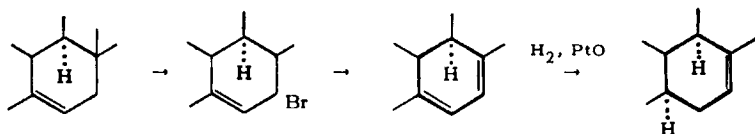
7-Dehydrosterols having the 5:6 and 7:8 ethylenic linkages also give 5,8-epidioxides when irradiated in the presence of oxygen:⁴⁸⁵



The 7:8 ethylenic linkage may be established by various methods. Catalytic reduction of a 7-carbonyl group in the presence of platinum and dehydration of the resulting 7-carbinol establishes a 7:8 olefinic bond:

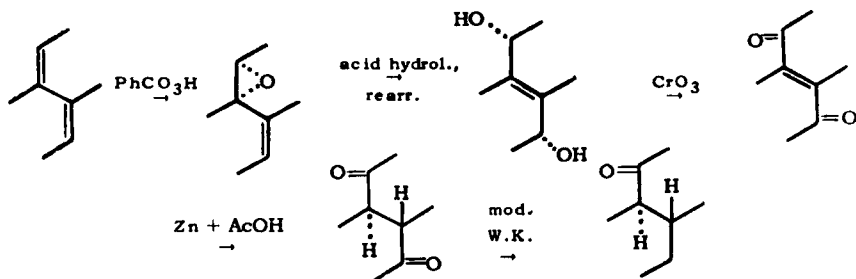


A 7-bromo compound results by the action of N-bromosuccinimide on a sterol with a 5:7 ethylenic bond, such as diosgenin; dehydrobromination produces a 7:8 ethylenic bond in addition to the existing 5:7 bond; the latter may be eliminated by selective hydrogenation:

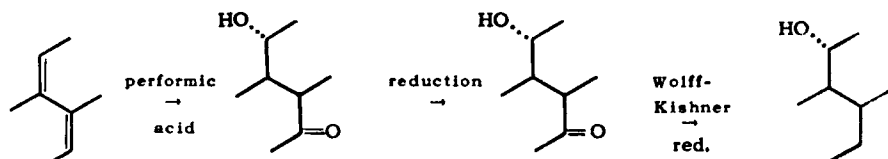


The presence of the 7:8, 9:11 conjugated dienes system in a steroid makes possible the introduction of a number of modifications in the molecule. Epoxidation of the 9:11 linkage, followed by hydrolytic rearrangement yields a 17:11-dihydroxy-8:9-ene; oxidation

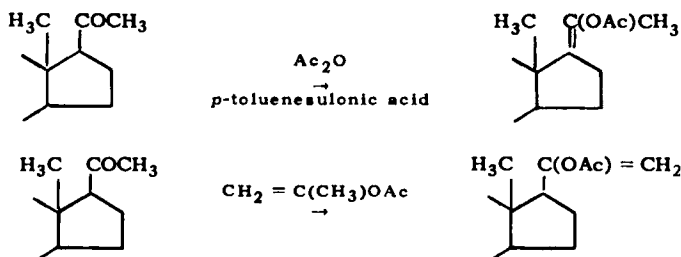
of the latter with chromic anhydride gives the corresponding 7:11-diketo body; reduction with zinc and acetic acid gives a saturated diketone; the modified Wolff-Kishner reduction converts the latter to the 11-monoketone:⁴⁸⁶



The 11-hydroxy group may be introduced by oxidation of the 7:8, 9:11-diene with performic acid to the 7-keto-9:11-oxido-8:9-ene, hydrogenation to the saturated hydroxy ketone and reduction of the latter by the Wolff-Kishner method:

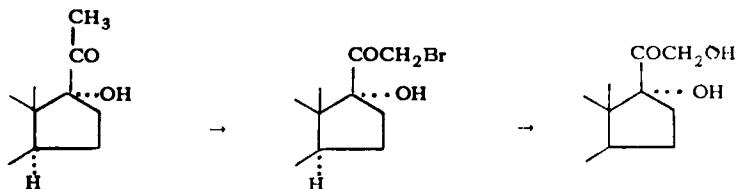


20-Ketones give a $\Delta^{17(20)}$ enol acetate with acetic anhydride-*p*-toluenesulfonic acid,²⁸⁰ but the isomeric Δ^{20} -enol acetates are formed with isopropenyl acetate:²⁸¹

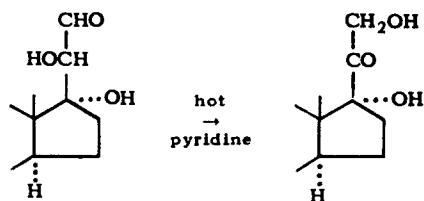


An 11-keto group gives an enol acetate with the former reagent but not with the latter. A 12-keto group fails to form an enolate with either reagent.

The methyl group at position 21 in allopregnan-2-one is brominated to the monobromo-methyl derivative, which may be converted to the hydroxymethyl derivative with caustic:⁴⁸⁷

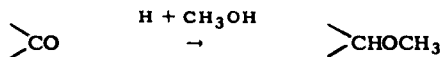


A hydroxyacetaldehyde group at position 17 has been converted to a hydroxymethyl group by a pinacolone rearrangement brought about by boiling with pyridine.⁴⁸⁸



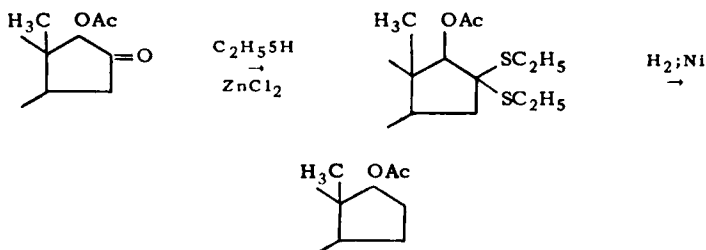
Carbonyl groups may be partially reduced to carbinol groups with sodium amalgam and alcohol, or with lithium aluminum hydride. Reduction with lithium in a mixture of liquid ammonia and alcohol appears to be of general applicability for the conversion of 11-keto steroids into the 11- α -hydroxy compounds.⁴⁸⁹ Sodium and propanol give similar results.⁴⁹⁰ Reduction with complex metal hydrides, and catalytic reduction yield mainly the β -epimer. Complete reduction of a keto group is effected by the Clemmensen method. Carbonyl groups at various positions in the sterol molecule are not equally reactive. Mild Clemmensen reduction of dehydrocholanic acid, which has carbonyl groups at 3, 7 and 12 positions, yields the 7,12-diketo acid.²⁸² Reduction with sodium amalgam gives 3-hydroxy-7,12-diketocholanic acid.²⁸³ The 7-carbonyl group in the compound is more readily reduced than the 12 carbonyl group; this same order of reactivity holds for acylation and hydrolysis reactions.²⁸⁴ The 3-keto group in pregnane-3,10,20-trione has been preferentially reduced to an α -carbinol with sodium borohydride in pyridine. The resulting compound has been converted to cortisone.²⁸⁵

3-Ketones undergo reductive methylation on catalytic hydrogenation in methanol in the presence of hydrobromic acid to form a methyl ether:²⁸⁶



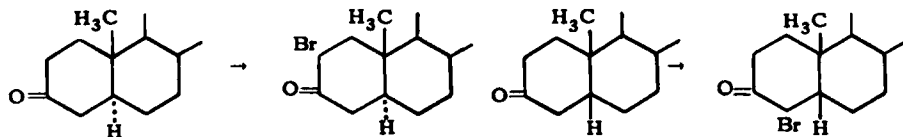
A carbonyl group may be selectively reduced in preference to a conjugated double bond or a carboxyl group by use of sodium borohydride. The conjugated double bond may, in turn, be reduced in preference to the carboxyl group by means of potassium and isopropyl alcohol in liquid ammonia, while the carboxyl group may be reduced with lithium aluminum hydride. An 11-ketone with unsaturated bonds at 8,9 position has been reduced to the saturated ketone with lithium and liquid ammonia, although reduction proceeded to the carbinol stage in the presence of ethanol.

Keto groups in the A and D rings react with ethyl mercaptan and ethylene 1,2-dithiol, HSCH₂CH₂SH, to form thioketals. Carbonyl groups in rings B and C react only with ethylene dithiol. An 11-keto group fails to react, however, with either of the mercaptans.²⁸⁷ The thioketals may be desulfurized by hydrogenolysis in the presence of Raney nickel. In the process, the sulfur atom is replaced with a hydrogen atom, so that the reaction offers an indirect method for the reduction of carbonyl groups:²⁸⁸



A keto group in a sterol may be protected from the action of certain reagents by conversion to a ketal.

Two methods for the introduction of ethylenic bonds in the molecule of a sterol have been mentioned. A further method consists in the bromination of the steroid followed by debromination or dehydrobromination. In the bromination of ketones related to sterols, compounds of the *trans* series give 2-bromo derivatives, whereas the corresponding *cis* compounds yield the 4-bromo isomers:

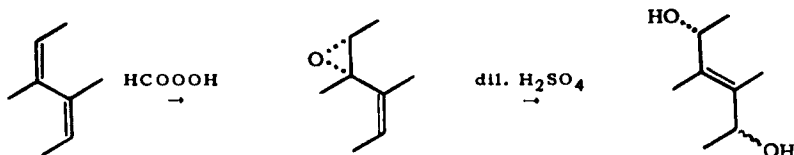


Analogous behavior is shown in the oxidation of such ketones.²⁸⁹ 2,2-Dibromocholestan-3-one may be rearranged to the 2 α ,4 α -dibromoketone by treatment with hydrobromic acid. Δ^4 -Cholestenone has been prepared through the debromination of the ketone obtained by the oxidation of cholesterol dibromide.²⁹⁰ Debromination is accompanied by migration of the double bond. Migration fails to occur when the debromination is carried out with zinc and acetic acid.²⁹¹ A 7,8-double bond may be introduced into a Δ^5 -steroid by the action of N-bromosuccinimide, followed by dehydrobromination.²⁹² A 7:8, 9:11-diene system has been established in the dihydroergosterol series by the addition of bromine at a 7,8-double bond and subsequent dehydrobromination with sodium iodide.²⁹³

Modifications Involving Unsaturated Bonds

Unsaturated bonds in a compound exhibit varying degrees of reactivity depending on the character of the compound and the position of the bonds in the molecule. They are more or less readily attacked by oxidizing agents. The oxidation of a 7:8,9:11-diene system in sterols has received considerable attention in efforts at interconversions of sterols, and more particularly in attempts at the synthesis of cortisone. Conversion of the system to a 7:11-dione is possible by various methods. The transformation has been brought about by direct oxidation with chromic acid.²⁹⁴ Oxidation with osmium tetroxide gives a glycol. The glycol resulting from the group $=C=CH_2$, namely $=C(OH)CH_2OH$, may be further oxidized with periodic acid to a carbonyl group $=C=O$.

Oxidation of the 7:8, 9:11-diene may be brought about by epoxidation with performic acid.²⁹⁵ The primary product of epoxidation in the 5- α -series would appear to be a 7-ene-9 α :11 α epoxide which rearranges to an 8:9-ene-7 ζ :1 α -diol under the action of dilute sulfuric acid:



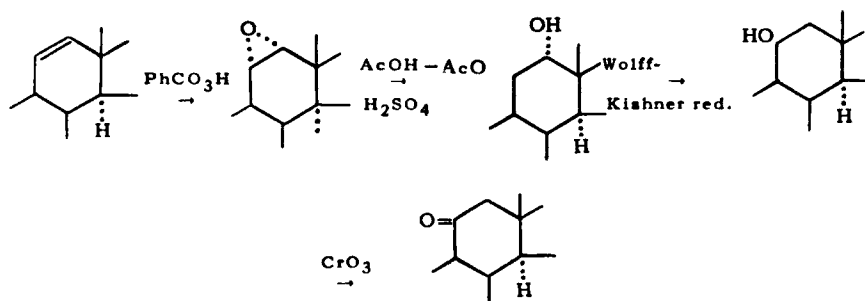
Under more drastic treatment the diol undergoes rearrangement to a 9:11-ene-7-one and finally to 8:9-ene-7-one. When the epoxide is treated with the boron trifluoride-ether complex, or with ferric chloride, it is converted to 8:9-ene-11-one:



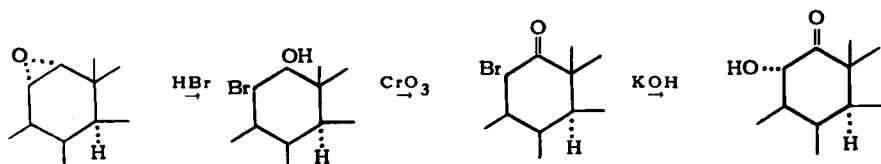
This can be reduced to the saturated ketone of natural configuration by treatment with

lithium and liquid ammonia. Reduction proceeds to the 11 α -ol stage in the presence of ethanol.

A keto group at 11 position has been produced utilizing a 11:12 ethylenic linkage by the following succession of steps: epoxidation, treatment with a mixture of acetic and sulfuric acids to obtain a monoacetylated glycol, oxidation with chromium trioxide to a 12-keto-11-acetoxy body, reduction of this by the Wolff-Kishner method to a 11-hydroxy compound and oxidation of the latter with chromium trioxide:⁴⁹¹

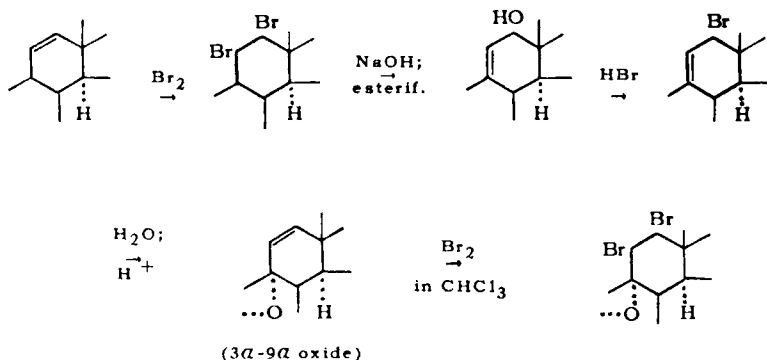


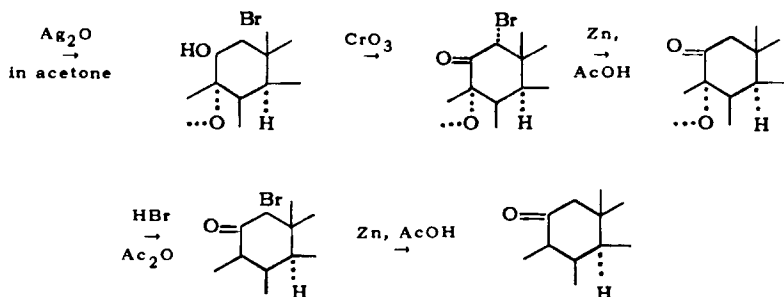
An 11-hydroxy-12-keto body is obtained from the epoxide by treatment with hydrogen bromide followed by oxidation with chromium trioxide and treatment with potassium hydroxide at 20°:



Under drastic conditions of reduction the 11-keto-12-hydroxy compound is formed.

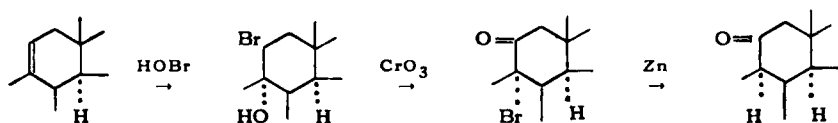
The conversion of methyl 3 α -hydroxychole-11-enate to the corresponding 11-keto cholic ester via the dibromide was effected in several steps, involving hydrolysis with caustic, esterification, treatment with hydrobromic acid followed by dehydrobromination, a second bromination and subsequent treatment with an acetone suspension of silver oxide, oxidation with chromium trioxide followed by treatment with hydrobromic acid acetic anhydride and finally reduction with zinc and acetic acid.⁴⁹² These steps are indicated below:





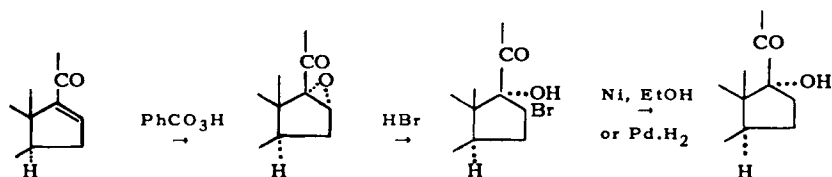
In the fourth step shown above, dehydrobromination involves passage via a mesomeric cation into a Δ^9 -3 α -9 α -oxide.⁴⁹³ This oxide junction is ruptured in the next to the last stage, restoring the hydroxyl group at position 3 α , which is acetylated at this stage.

A 9:11 ethylenic linkage may serve for the establishment of a carbonyl group at position 11. This has been accomplished with 3 α -acetoxychole-9(11)-en-3-ol by treatment with hypobromous acid and subsequent oxidation with chromium trioxide to an 11-keto-9 α -bromide from which the bromine is removed by treatment with zinc.⁴⁹⁴



The method has been employed in the total synthesis of cortisone from the synthetic steroid methyl Δ^9 -3 α -acetoxyethiocholanate.⁴⁹⁵

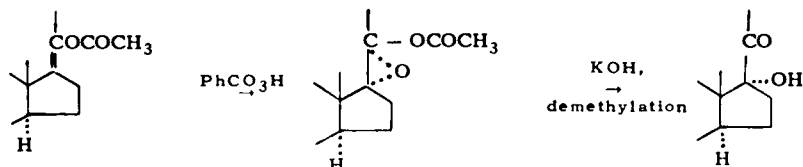
Introduction of an α -OH group at position 17 by utilization of a 16:17 ethylenic bond may be accomplished by treatment with perbenzoic acid followed by reduction with Raney nickel in ethanol, or catalytically with palladium:



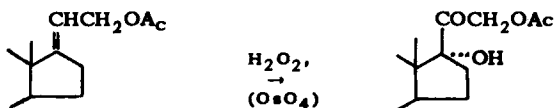
Reduction of the glycol acetal of the epoxy compound with LiAlH_4 also yields the 17 α -hydroxy derivative.

A side-chain unsaturation in a sterol, such as is present in ergosterol, may be protected during the course of treatments by selective bromination. The unsaturated bond is regenerated by debromination after the conclusion of the series of modifications.

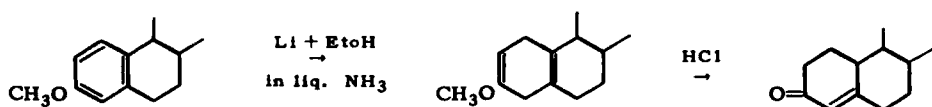
The 17:20 double bond in sterols appears to be epoxidized in preference to a double bond in a ring. By epoxidation of this bond and subsequent hydrolysis, a 17-hydroxy-20-keto body has been obtained from one with an acetoxy group attached to position 20:⁴⁹⁶



Treatment of $\Delta^{14,17}$ -pregnanedien-2-ol-3-one with hydrogen peroxide in the presence of a small amount of osmium tetroxide brings about the entrance of a hydroxyl group at position 17 and oxidation of the C20 to a keto group giving the acetate of Reichstein's compound:⁴⁹⁷



The reduction of phenol ethers to their dihydro derivatives has been brought about with lithium in liquid ammonia, and the method has been used to effect the synthesis of 19-nortestosterone from oestradiol methyl ester, decomposition of the dihydrophenyl ether with hydrogen chloride resulting in the formation of the 3-keto-4,5-unsaturated compound:⁴⁹⁸



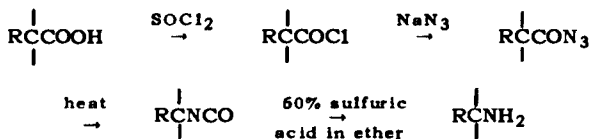
Bromination of 24,24-diphenyl-23-enes with N-bromosuccinimide takes place at position 22; that of 23,23-diphenylnorchol-22-ene at position 20, while that of 24,24-diphenylchola-20,23-dienes occurs at position 21. 22,22-Diphenylbischol-20-ene is not brominated by bromosuccinimide.⁴⁹⁹

Miscellaneous Modifications – Degradative Methods

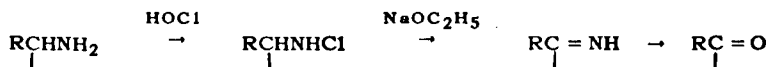
The 11 α -position in progesterone may be hydroxylated biosynthetically by *Rhizopus nigricans*.²⁸⁵

Cholic acid is selectively oxidized at 7-position with chromium trioxide in acetic acid at -7 to 0° .²⁹⁶

Carboxyl groups attached to a side chain may be replaced with an amino group by a modified Curtius degradation:²⁹⁷



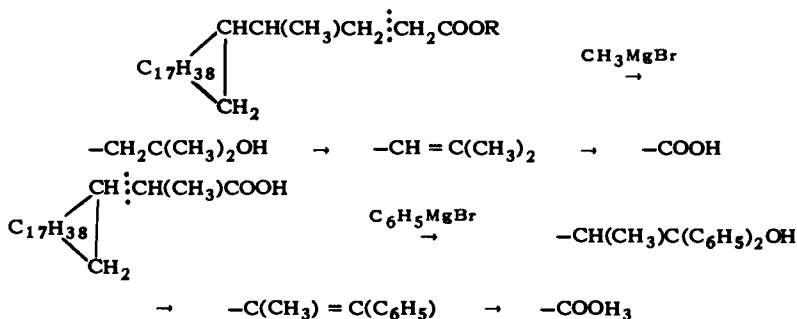
The amino group may be transformed to an imino group by treatment with ethereal hypochlorous acid at 0° followed by treatment with sodium ethoxide. Hydrolysis causes the replacement of the imino group with oxygen, yielding a ketone.



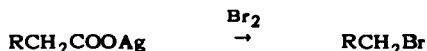
Pregnanolone was prepared by this method from hydroxybischolonic acid.

The Barbier-Wieland degradation makes possible the shortening, by one carbon atom at a time, of a side chain carrying a carbonyl group at the end.²⁹⁸ Degradation of cholan-ic acid to norcholan-ic acid and of the latter successively to bisnorcholan-ic acid and etiocholan-ic acid has been carried out by this method. The first two steps of the conversion were effected by the reaction of methylmagnesium bromide with the ester of the acid; the hydroxy compound obtained by hydrolysis, dehydrated to an olefin acid,

was oxidized to an acid with one carbon less. For the third stage, the ester of the acid was reacted with phenylmagnesium bromide, the resulting diphenylcarbinol was dehydrated and once more oxidized to obtain etiocholy1 methyl ketone:



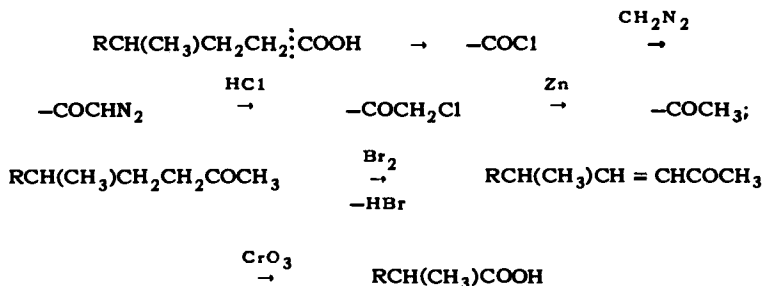
Treatment of the silver salt of the acid with bromine eliminates the carboxyl group:²⁹⁹



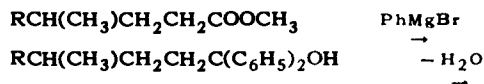
Reduction of the resulting bromo compound with zinc and acetic acid yields the hydrocarbon RCH_3 .

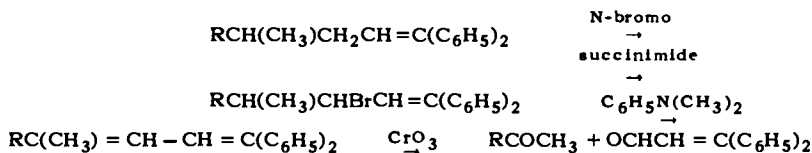
Cholane, $\text{C}_{24}\text{H}_{42}$, the basic hydrocarbon of the bile acid series, has been prepared by the Clemmensen reduction of bisnorcholyl methyl ketone which was obtained as a by-product of the second oxidation.

Another method of degradation which decreases the length of a side chain with a carboxyl group at the end by two carbon atoms, makes use of the reaction of the chloride of the acid with diazomethane. The successive steps are conversion of the diazo ketone to the chloroketone by reaction with hydrochloric acid; reduction of the chloromethyl group to a methyl group with zinc, bromination followed by dehydrobromination to obtain an unsaturated ketone, and finally oxidation with chromium trioxide to an acid:³⁰⁰

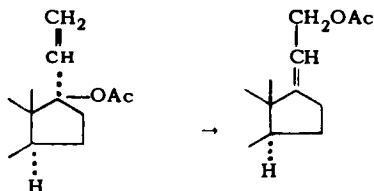


Another method based on the Grignard reaction makes possible the removal of three carbon atoms at once (*Miescher-Wettstein degradation*).³⁰¹ The ester is made to react with phenylmagnesium bromide; the hydroxylated diphenyl derivative resulting from the hydrolysis of the complex formed is dehydrated and subjected to the action of N-bromosuccinimide. The bromo compound formed is dehydrobrominated and, subsequently oxidized with chromium oxide at 0° :

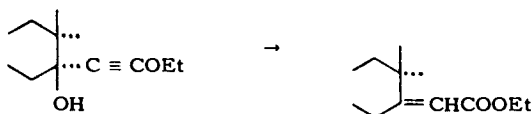




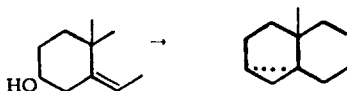
Many structural changes have been produced in the molecule of steroids through molecular rearrangements. The transformation of 7-ene-9 α :11 α -epoxides to 8,9-ene-11-ones by treatment with boron trifluoride-ether complex has been mentioned. An anionotropic rearrangement takes place in a 17 α -ethylene-17-acetoxysterol to a 21-acetoxy-20-ene



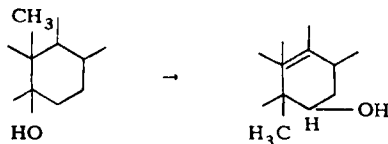
A similar migration has been observed in an acetylenic compound:⁵⁰⁰



A cyclosteroid may form through the molecular rearrangement of a 3 β -hydroxy- Δ^5 -steroid:



In the *Westphalen rearrangement*, which takes place under the action of sulfuric acid, an angular methyl group in a 5 α -hydroxy steroid migrates from position 10 to position 5, and simultaneously the elements of water are eliminated with the appearance of a 9:10 ethylenic linkage, as with 5-methyl-19-norcholest-9(10)-ene-3 β : 6 β -diol:⁵⁰¹



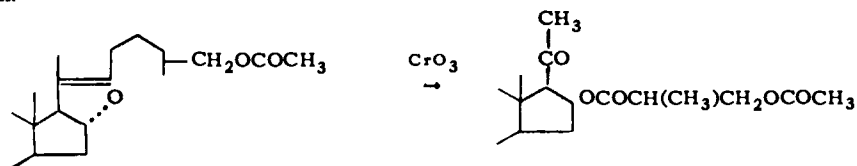
The rearrangement appears to be general for α -hydroxy steroids.

A similar rearrangement involves the migration of an angular 18 methyl group to position 17, and simultaneous dehydration with removal of a hydroxy group attached to C17 and appearance of a 14:18 ethylenic linkage:



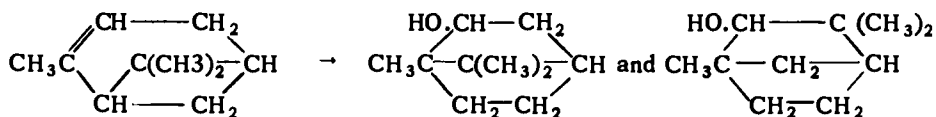
The appearance of an ethylenic bond in the side chain of a sterol may be followed by

oxidative rupture of the bond and the formation of a carbonyl compound. An example is found in the formation of an intermediate in the synthesis of cortisone from hecogenin:⁵⁰²

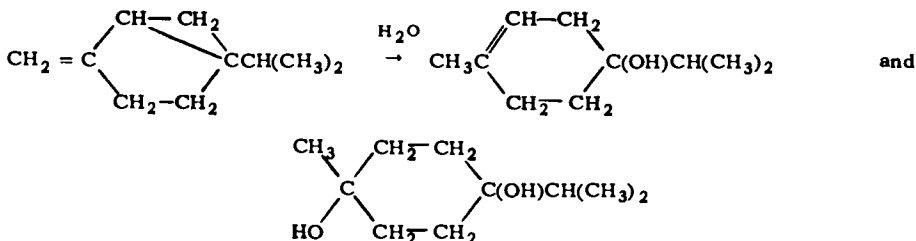


Molecular Rearrangements

Many terpenes show a ready tendency to undergo isomerization under the action of certain chemical reagents, particularly acids. Isomerization may take place also on subjecting the compound to the action of comparatively high temperatures, especially in the presence of catalysts. Isomerization may often take place during the course of a reaction. Molecular rearrangements occur, for example, when α -pinene is hydrated, giving borneol or fenchyl alcohol:



Sabinene, shaken with dilute sulfuric acid, passes readily into terpin-4-ol and 1,4-terpin:⁸⁰

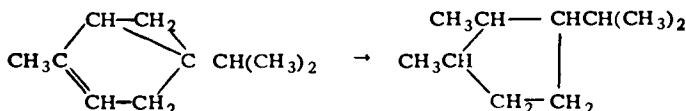


The dehydration of isoborneol leads to the formation of camphene, while camphene hydrochloride is readily isomerized to isobornyl chloride.

The *thermal* isomerization of α -pinene in the vapor or liquid phase, preferably over copper or other catalyst, results principally in the formation of dipentene and alloocimene, the yield of the latter amounting to 50% under favorable conditions.⁸¹ Considerable quantities of α - and β -pyrenonea may also be formed by the further isomerization of alloocimene.

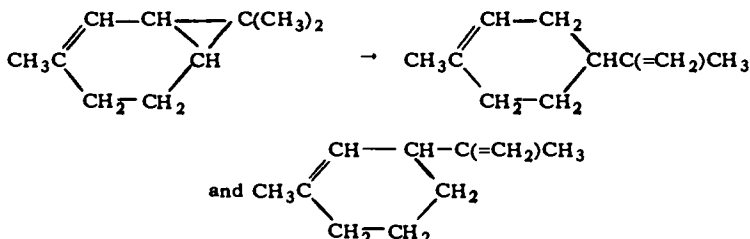
It has been claimed that α -pinene may be converted to camphene in 70% yield by refluxing the hydrocarbon over a clay catalyst.⁸²

α -Thujene is converted largely to 1,2-dimethyl-3-isopropylcyclopentane when it is distilled over nickel in a current of carbon dioxide:⁸³

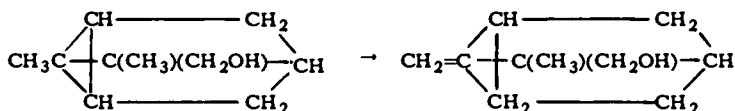


The purely thermal rearrangement of azulene to naphthalene has been brought about by heating at 330°. ⁸⁴

Carene is readily isomerized by dilute acids to a mixture of dl-limonene and sylvestrene:



dl-Teresantalol, treated with sulfuric acid, gives apocamphene carbinol:



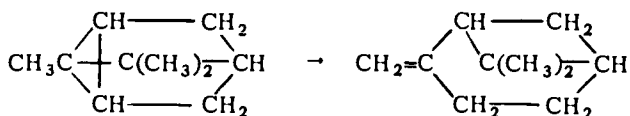
β -Pinene is converted to α -pinene to the extent of 70% when heated with resin at 60° for 15 to 20 hours. ⁸⁵ A similar isomerization takes place when β -pinene is shaken with platinum black previously saturated with hydrogen. ⁸⁶

Camphene hydrochloride is remarkably stable in ethereal solution, while in nitrobenzene the compound undergoes transformation into isobornyl chloride, 50% of the compound being thus converted to the latter in 1½ hours at 20°. The reaction velocity is related directly to the dielectric constant of the solvent. A marked influence is also exerted by catalysts, the rate of transformation being enormously increased, for example, by the addition of stannous chloride, hydrogen chloride, phenols, etc. ⁸⁷

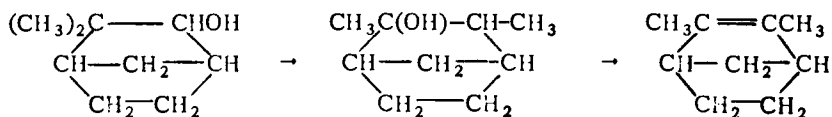
The transformation of 1-menthone into d-menthone has been achieved by dissolving the compound in concentrated sulfuric acid and pouring the solution on ice. ⁸⁸

Wagner and Nametkin Transformations

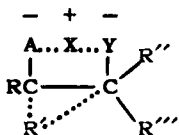
Many of the molecular rearrangements which terpenes have been observed to undergo may be classed under the Wagner or the Nametkin transformations. The former may be exemplified by the conversion of tricyclene to camphene: ⁸⁹



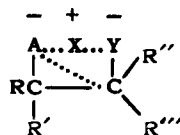
The rate of transformation in a given solvent appears to be in proportion to the dielectric constant. The Nametkin transformation involves a pinacone-pinacol type rearrangement, and may be exemplified by the formation of santene from camphenilol: ⁵¹⁶



Robinson⁹⁰ has pointed out the correlation of the Wagner and Nametkin transformations on the basis of the electronic theory. Assuming X to represent an electropositive group or element and Y an electronegative unit in $RR'C(AX).CYR''R'''$, and assuming further that junction takes place by means of partial valencies, then there arises "conjugation" and the conditions represented by (a) and (a') hold:



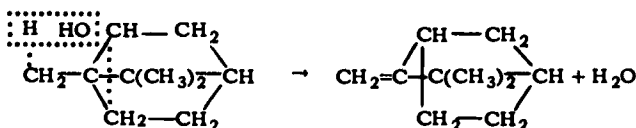
(a)



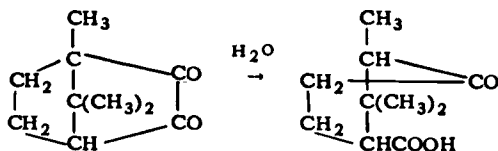
(a')

If XY separates from (a) the compound $RC(A)-CR''R'''$ will be formed, while if it separates from (a') the compound $RR'C.C(R'')(R''').A$ will be obtained, the former representing the Wagner transformation, the latter the Nametkin rearrangement. The reaction is probably not direct, but takes place by an ionic mechanism.

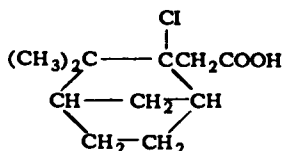
The Wagner transformation may be further illustrated by the conversion of isoborneol to camphene:



A change related to the Wagner rearrangement is undergone by camphorquinone in the presence of sulfuric acid, giving rise to a ketonic acid:³⁰²



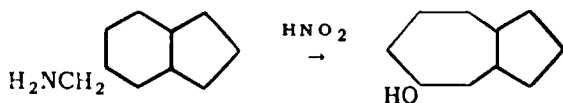
The chloroacid



shows no tendency to undergo the Wagner rearrangement due, apparently, to the presence of the carboxyl group in the side chain. Camphene-1-carboxylic acid undergoes the transformation readily.

Other Rearrangements

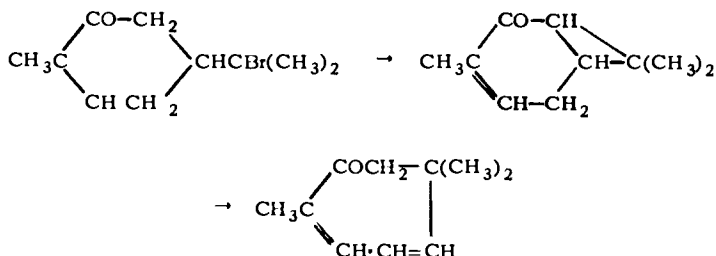
Molecular rearrangements leading to ring enlargement have been observed in special cases. Thus, hydrindylmethylamine treated with nitrous acid undergoes ring enlargement yielding bicyclo-(5,3,0)-decan-5-ol:



This transformation is known as the *Demjanov rearrangement*.

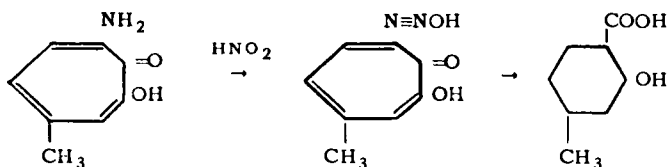
The formation of seven membered rings from benzene derivatives, by reaction with diazoacetic ester followed by heating at 160 to 165°, also presents an example of the same type of transformation.

Ring enlargement occurs when carvone hydrobromide is treated with an alcoholic solution of potassium hydroxide and eucarvone is formed:⁹¹



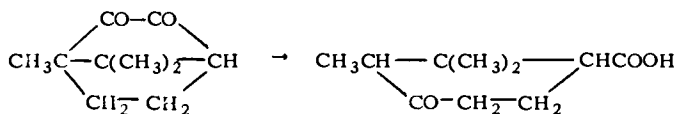
A benzo- γ -tropolone has been obtained by a similar transformation of a hydroxyphenyl-hydroxymethyl derivative of anthraquinone.³⁰³

The reverse rearrangement giving rise to benzene derivatives from tropolones has been accomplished. α -Amino tropolones have been transformed into derivatives of salicylic acid by diazotization:³⁰⁴

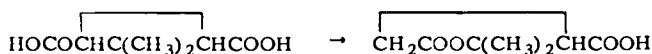


α - γ -Dinitro- β -isopropyltropolone is converted to a dinitroisopropylbenzoic ester simply by crystallization from an alcohol.³⁰⁵

Ring cleavage and ring enlargement occur simultaneously when camphorquinone is dissolved in concentrated sulfuric acid, giving *d*-2,2,3-trimethylcyclohexan-4-one-1-carboxylic acid:⁹²



Caronic acid has been isomerized to terebic acid by heating with hydrobromic acid at 100°:⁹³



Separation and Purification of Products

Special methods of treatment are often necessary for the isolation of the cyclic products resulting from a particular method of synthesis.

The purification of *piperitonea*, *d-pulegone* and *1-menthene-3-one* has been effected via the corresponding alcohols, which may be prepared in a state of purity by one or more of the following methods:

Fractionation of the acid phthalate of the alcohol.

Fractional esterification.

Fractional saponification of esters.

Treatment of the pure amine hydrochlorides with nitrous acid, the amines being obtained by distilling the ketone with ammonium formate,⁹⁴ or by reducing the oxime with sodium and alcohol.⁹⁵

Fenchosantenone and *fenchone* may be separated by taking advantage of the difference in the rate of reaction of these ketones with semicarbazone, the former reacting with this reagent very rapidly, the latter quite slowly.

The stable modification of *isonitrosocamphor* has been obtained pure and free from the lower melting unstable isomeride by fractional crystallization or by treatment of the crude isonitroso derivative with ferric chloride in ethereal solution.⁹⁶

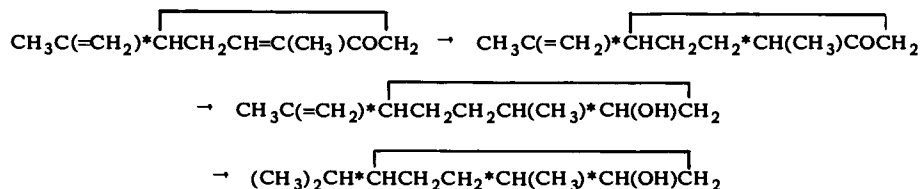
Camphoric acid may be separated from *isocamphoric acid* by treatment with acetyl chloride, whereby camphoric acid is converted into its anhydride, while isocamphoric acid remains unaffected and may be separated by treatment with cold dilute caustic solution.

The separation of *stereoisomeric* forms of terpenes has been effected in many cases by the usual methods. Thus, 1-isoborneol has been isolated from the pure 1-menthylamine salt of its hydrogen phthalate obtained by fractional crystallization, while the dextro isomer is similarly obtained from the cinchonine salt of its hydrogen phthalate.⁹⁷

dl-Camphor has been resolved into its enantiomorphs by fractional crystallization.⁹⁸

The resolution of *dl-menthola* has been accomplished by conversion to glucoisides, maleate, or the tartranilic ester.⁹⁹ The resolution has been accomplished on the large scale by use of *1-menthoxyacetic acid* or *1-menthylglycine*, by converting the compound into the ester of these acids.¹⁰⁰

The stereoisomerides of carvomenthol have been successfully separated by isolating the isomers of the intermediates in the reduction of carvone through dihydrocarvone, carveol, and dihydrocarveol to carvomenthol:



Proceeding in this manner, the number of asymmetric carbon atoms, indicated by asterisks, is increased one at a time, and it is a comparatively simple matter to separate the stereoisomers at any one stage.¹⁰¹ Certain of the stereoisomers have also been prepared from the corresponding carvomenthylamines.¹⁰²

The two stereoisomerides of the 3-ethylene ketal of 11-ketoprogesterone have been

isolated as the strychnine salt of the 21-oxalyl acid. The + acid has served as an intermediate in a synthesis of cortisone.²⁰⁹

Some Characteristics of Carbocyclic Compounds

Cyclopropane behaves in many of its reactions like an ethylenic group; the analogy extends even to the spectra of derivatives of cyclopropane and ethylene.

From a study of absorption spectra it has been concluded that the *cyclopropane* ring is a center of residual affinity similar in character but intermediate in quantity to that of the double bond, and as such can form a conjugated system with the carbonyl group.¹⁰³

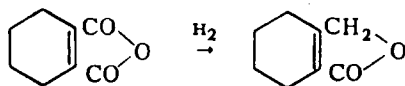
The absorption spectrum of umbellone is quite different from that expected of a simple α,β -unsaturated ketone, due to the cross-conjugation of the cyclopropane ring with the carbonyl group and the ethylenic linkage.

Substituents have exactly the same effect upon the mode of addition to a cyclopropane ring as to an ethylenic linkage, even though the saturated open chain compounds formed in the two cases are quite different in structure.¹⁰⁴

The molecular refraction of thujyl alcohol shows a marked exaltation owing to the presence in the molecule of the cyclopropane ring.

According to the Staudinger-Schmidt rule the 3:4 carbon bonding in cyclobutene is under the weakening influence of the π -electron system of the double bond from both sides. The thermal instability of the ring is intensified by ring strain and the one-sided accumulation of atoms of hydrogen. Negative substituents at 3 and 4 positions further decrease ring stability; positive substituents, such as alkyl groups have the contrary effect. Diphenylene (dibenzylcyclobutadiene) is a markedly stable compound.⁵³⁷ Contrary to the Staudinger-Schmidt rule, bicyclo(4,2,0)octadiene-2,7 does not show any tendency to isomerize to cyclooctatriene.⁵³⁸

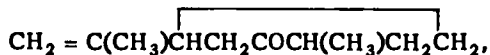
The unsaturated bonds in cyclohexenes are characterized by their great reactivity; they add nitrosyl chloride and nitrogen oxides to form nitrosochlorides, nitrosites and nitrosates. They form epoxides by reaction with benzoyl peroxide.³⁰⁶ Some cyclohexenes react with phenol in the presence of glacial acetic and sulfuric acids to form cyclohexylphenols.³⁰⁷ In Δ^1 -tetrahydrophthalic anhydride, however, the unsaturated linkage is inactive, since it is sterically protected, and reduction of this compound affords the phthalide and not hexahydrophthalic anhydride:



The Δ^1 -tetrahydro acid and Δ^4 -tetrahydro anhydride are hydrogenated to the hexahydro stage.

Whereas unsaturated cyclic hydrocarbons are more stable than the corresponding saturated cyclic substances, they oxidize readily and tend to isomerize and polymerize, especially when distilled at atmospheric pressure. Cyclopropane

polymerizes very readily. Substances containing conjugated double bonds resinify or polymerize on standing in the air or on warming with metallic sodium. The ethylenic linkage in dihydrocarvone,



is somewhat labile and shows a tendency to pass into the ring with the formation of the isomeric ketone carvenone.¹⁰⁵

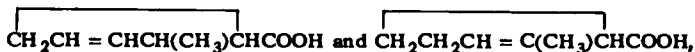
A compound possessing a *cis* configuration always has a higher density and refractive index than its *trans* isomeride.¹⁰⁶ This is the important *Auwers-Skita rule*. Sterols of *cis* configuration, in contrast to their *trans* isomers, yield insoluble compounds with digitonin.

It is noteworthy that the optical rotatory power of active saturated hydrocarbons is usually much lower than that of the unsaturated hydrocarbons of the same carbon atom structure.

The *five-atom ring* structure in isothujone, $(\text{CH}_3)_2\text{CHCHCH}_2\text{COC}(\text{CH}_3)=\text{CCH}_3$, has been shown to cause a pronounced deviation in the wavelength of maximum absorption.

The four carbon ring in pinocampene is more stable than that in the unsaturated ketone carvopinone. The same stability is noted in the corresponding alcohol.¹⁰⁷

Of the two acids 1-methyl- Δ^4 - and 1-methyl- Δ^5 -cyclohexenylcarboxylic acids,

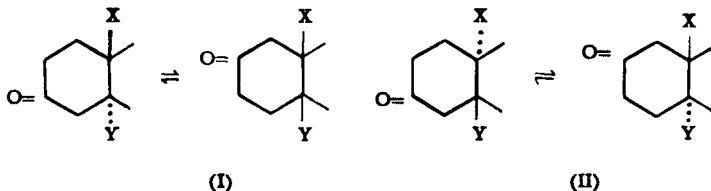


the former esterifies more rapidly than the latter. The ester of the former acid hydrolyzes more readily than that of the latter.

In the case of similar unsymmetrical acids, treatment of the anhydride with sodium alkoxide causes esterification of the carboxyl group attached to the least substituted α -carbon atom,¹⁰⁸ and partial hydrolysis of the neutral esters always results in the preferential hydrolysis of the α -carboxyl group.¹⁰⁹

When amides or alkyl amides of acids in which the carboxyl group is attached to a tertiary carbon atom are treated with phosphorus pentachloride, a chloroimide is formed. The acid is obtained from the chloroimide by treatment with water.

The molecular rotation contribution of a terminal ring in a triterpene is, in the main, independent of the rest of the molecule, providing the penultimate ring is saturated and unsubstituted.³⁰⁸ For each type of terminal unit, the molecular rotation contribution has a characteristic magnitude. Taking the two enantiomorphous forms of a *trans*- β -decalone (I) and (II)



as an example, the molecular rotation contribution, taken as the difference

$$M_D 1 \text{ of ketone} - M_D 1 \text{ desoxy compound}$$

is approximately the same when X and Y are hydrogen or alkyl groups.

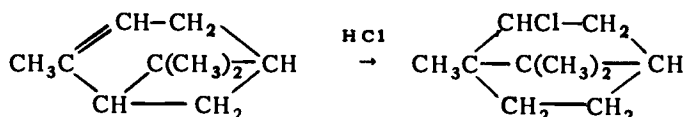
Naturally occurring terpenes are built up of isoprene units of five carbons each. This is known as the *isoprene rule* and is probably significant as an indication of the origin of these bodies. There are, it is true, naturally occurring compounds unquestionably related to terpenes which do not contain an even multiple of isoprene units, but these compounds have most likely been derived from terpenes with an even number of isoprene units by a process of degradation.

A modified form of the rule known as the biogenetic isoprene rule has been introduced by Ruzicka,⁵⁰³ which states that the carbon skeleton of naturally occurring terpenoids are formed from a limited number of isoprenoid precursors, possibly geraniol, farnesol, geranylgeraniol and squalene.

Reactions of Cyclic Hydrocarbons

Reactions with Hydrogen Halides

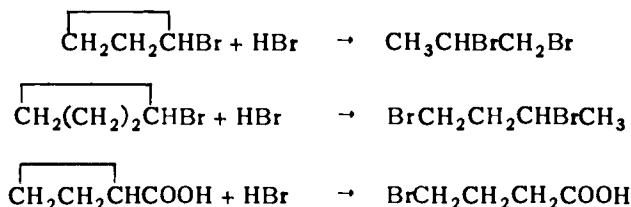
Hydrogen chloride and hydrogen bromide add in a normal manner at the double bonds of many unsaturated cyclic compounds. Molecular rearrangements may be induced, however, under the action of hydrogen halides in compounds capable of isomerization. Thus, α -pinene is converted into bornyl chloride by the action of hydrogen chloride:



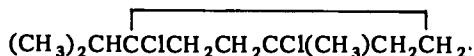
β -Pinene treated with hydrogen chloride at a low temperature is converted into pinene hydrochloride, and this, on treatment with aniline, gives pinene.¹¹⁰

Unstable carbon ring structures are often ruptured by hydrogen halides. Pinene in acetic acid solution gives mainly dipentene hydrochloride with rupture of the bridge or cyclobutane ring.

Bromocyclopropane, bromocyclobutane and cyclopropylcarboxylic acid are converted into open chain compounds by concentrated hydrobromic acid:¹¹¹



The mode of addition of hydrobromic acid to cyclopropane hydrocarbons is determined by the number and arrangement of the alkyl groups. The ring invariably opens between the carbon atoms that hold the largest and smallest number of alkyl groups, and the principal product is always one in which the halogen is combined with the carbon atom that holds the largest number of alkyl groups. The cyclopropane ring in α -thujene is unstable and readily undergoes cleavage under the action of hydrogen chloride in acetic acid solution, giving the corresponding terpinene dichloride,



Hydrogen chloride reacting with d- or l-limonene in the presence of moisture gives dipentene dihydrochloride.¹¹²

Reaction with Halogens

The photochemical halogenation of cyclopropane yields principally 1,1-dichlorocyclopropane, with some of the 1,2-dichloro isomer. Cyclohexane is not acted upon in the cold by bromine and reacts very slowly at its boiling point and in diffuse sunlight with this halogen. The bromination of the hydrocarbon in the presence of anhydrous aluminum chloride results in the formation of high boiling products.¹¹³ Cyclohexane reacts readily with dry chlorine even in the absence of sunlight. Two chlorides are first formed which decompose extensively on distillation at atmospheric pressure. On long continued chlorination tetrachlorocyclohexane is formed.¹¹⁴ Chlorination of methylcyclohexane gives 60% of 1-methyl-3-chlorocyclohexane and 40% of the 1,2-derivative.

Thujane reacts with bromine to give a dibromide, addition being evidently accompanied by ring fission.¹¹⁵

In the halogenation of cyclic ketones, the halogen always enters at the α -position with respect to the carbonyl group. Thus, camphor gives with chlorine α -chlorocamphor,⁵¹⁷ and methone gives 4-chloromenthane-3-one.¹¹⁶ ω -Chlorocamphor has been obtained by the action of chlorine on 1-hydroxycamphene in a mixture of acetic acid and sodium acetate.⁵⁰⁴ π -Chlorocamphor results on heating camphor π -sulfonyl chloride to 150°.

Unsaturated cyclic compounds in general react normally with chlorine and bromine. Anomalies are observed in some cases. For example, 2-cyclopropane-1,2-propene, $\text{CH}_2\text{CH}_2\text{CHC(=CH}_2\text{)CH}_3$, reacts with bromine to give the tri-

bromide $\text{CH}_2\text{CH}_2\text{CBrCBr(CH}_3\text{)CH}_2\text{Br}$. d - Δ^3 Carene reacts with bromine readily in chloroform solution, absorbing one molecule of the halogen, although the dibromide formed is unstable and loses one molecule of hydrogen bromide.

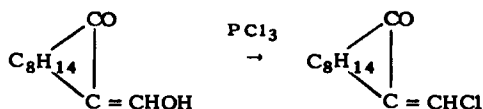
Treatment with alkalis, of the halides resulting from the reaction of unsaturated terpenes with halogenes does not always give the expected product, pulegone dibromide yielding, for example, the sodium salt of an acid,

$\text{HO} \overbrace{\text{COCHCH(CH}_3\text{)CH}_2\text{CH}_2\text{C}} = \text{C(CH}_3\text{)}_2$. The free acid loses carbon dioxide to form pulegene.¹¹⁷

Replacement of an oxygen atom or a hydroxyl group with chlorine may be achieved by treatment with phosphorous chlorides or oxychloride.

Thus, 1-camphor treated with phosphorus pentachloride gives the dextrarotatory α -dichloride. Dehydrochlorination of this with potassium acetate yields α -chlorocamphene, which has formed the basis for the synthesis of d -camphor.¹¹⁸

Hydroxymethylene camphor treated with phosphorus trichloride or oxychloride gives chloromethylenecamphor:



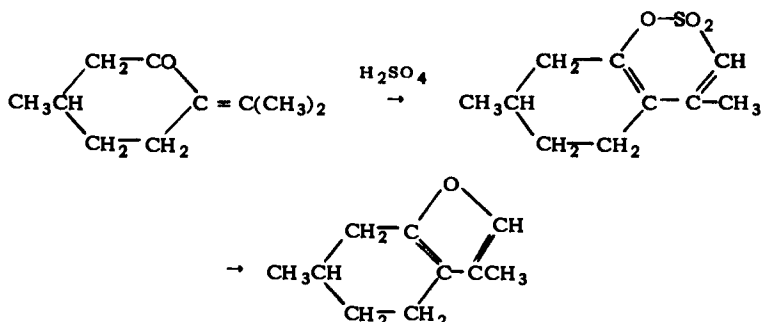
The chloride reacts with alkylmagnesium halides to form alkylidene camphors. This offers a simple method for the preparation of these derivatives of camphor.

Menthol treated with phosphorus trichloride gives menthyl chloride and 1-trimethyl phosphite, $\text{P}(\text{OC}_{10}\text{H}_{19})_3$. With phosphorus oxychloride, trimethyl phosphate is obtained.¹¹⁹

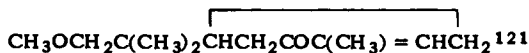
Reaction with Sulfuric Acid

Saturated cyclic hydrocarbons are, in general, stable toward sulfuric acid. Compounds containing conjugated diene groups react vigorously with concentrated sulfuric acid with the formation of tarry products.

A unique behavior is shown by pulegone toward sulfuric acid in the presence of acetic anhydride, the reaction resulting in the formation of a pulegenol sulfuric cyclo ester, which loses sulfur dioxide to form an oxide:¹²⁰



The exocyclic ethylenic linkage in *carvone* reacts in an unusual manner with methanolic sulfuric acid, forming the ether



Dihydrocarvone behaves in a similar manner, but carvotanacetone is unaffected by this treatment.

Camphor may be sulfonated in acetic anhydride solution to give the ω -sulfonic product (I)⁵⁰⁵ Sulfonation with fuming sulfuric acid, chlorosulfonic acid, or methyl chlorosulfonate proceeds with racemization and the formation of \pm camphor- π -sulfonic acid (II)



The chlorides and bromides of π -sulfonic acids, heated at 150° , give the π -chloro and -bromocamphors.⁵⁰⁶ The halide is converted to *trans*- π -hydroxycamphor on treatment with potassium acetate followed by hydrolysis.

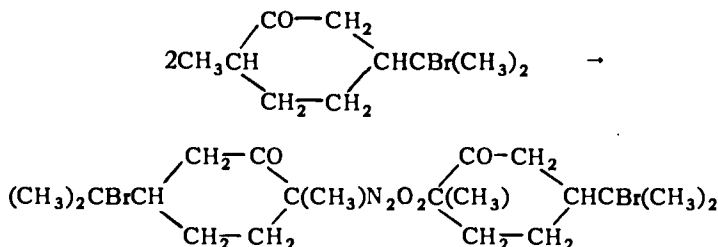
Certain terpenes are hydrated readily on treatment with sulfuric acid. Limonene is converted to α -terpineol, for example, when shaken with a dilute solution of sulfuric acid in acetic acid, some terpin hydrate being formed at the same time. The latter is obtained in excellent yield when the terpene is treated with 50% sulfuric acid at -6° .¹²² *Cis*-terpene hydrate is obtained from pinene by treatment with 25% sulfuric acid.¹²³ This hydrate can also be prepared from pinene by use of other acids, such as benzene sulfonic, benzoic acids, etc.¹²⁴ α -Pinene may be transformed to terpeneol by boiling with dilute acids; refluxing with clay transforms the former into α -terpinene and terpinolene.¹²⁵ α -Terpineol has been obtained directly from turpentine (pinene) through the action of sulfuric acid in alcoholic or acetic acid solution.¹²⁶ α -Pinene is hydrated more slowly than β -pinene, giving higher yields of monocyclic derivatives.¹²⁷ 1,4-

Terpin, $\text{CH}_2\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)_2$, results when sabinene, α -thujene or terpinene-4-ol are hydrated with dilute sulfuric acid.¹²⁸

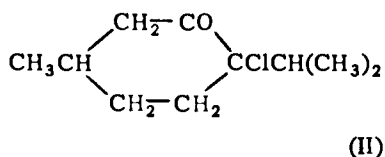
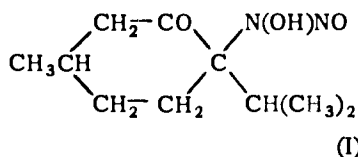
Verbenone undergoes cleavage on hydration with dilute sulfuric or hydrochloric acid, giving Δ^1 - α -menthen-3-one.

Nitrosates, Nitrosochlorides, etc. Derived from Terpenes

Bimolecular nitroso derivatives of terpenes have been prepared by treating these compounds with ethyl nitrite and acetyl chloride.¹²⁹ A nitroso compound was obtained by this treatment from dihydrocarvone hydrobromide:

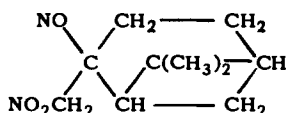


These compounds are, in fact, bis-nitrosanitrosites. A crystalline bis-nitrosanitrosite has been obtained by this method from menthone. Hydrolysis of this nitrosite with hydrochloric acid gives a nitrosylic acid (I) and a chloro-ketone (II).

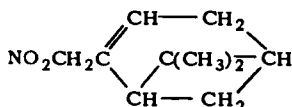


A bis-nitrosocarone has also been obtained from carone.¹³⁰

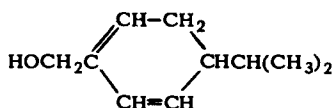
Pinene nitrosite is obtained through the reaction of nitrous acid with oil of turpentine.¹³¹ This compound has the structure



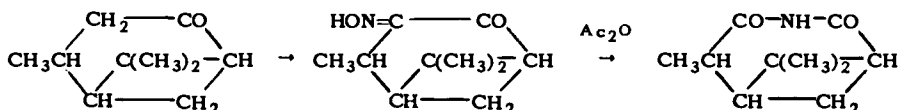
When distilled with steam it gives "nitroterebenthine"¹³²



Reduction of this compound with zinc dust and acetic acid results in the formation of the corresponding amino compound, and treatment of the latter with nitrous acid gives a monocyclic alcohol,



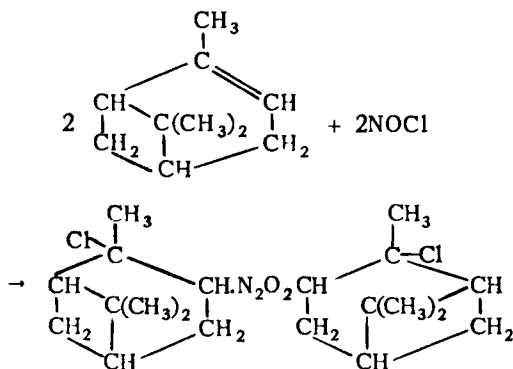
Verbenone, reacting with isoamyl nitrite in the presence of sodium amide, gives an oximino derivative which is converted with acetic anhydride into the imide of pinocamphoric acid:



Similarly epicamphor reacts with isoamyl nitrite in the presence of sodium amide to form isonitroso-1-epicamphor, which exists in two modifications.¹³³

Sodio camphor treated in ethereal solution with isoamyl nitrite, gives isonitroso-camphor, $\text{C}_8\text{H}_{14}\text{COC} = \text{NOH}$,¹³⁴ together with a base, $\text{C}_8\text{H}_{14}\text{CONHC} = \text{NH}$.

Nitrosochlorides result through the reaction of nitrosyl chloride with terpenes with unsaturated bonds. Pinene nitrosochloride is obtained in very high yield through the reaction of nitrosyl chloride with the terpene in solution in a mixture of equal volumes of ether and acetic acid cooled with ice-salt mixture.¹³⁵

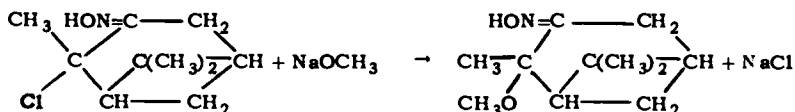


The compound can be purified by crystallization from benzene or chloroform solution, but it is decomposed when heated for any length of time with either of these solvents.

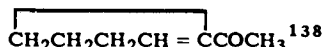
Nitrosyl chloride may be prepared conveniently by dropping concentrated sulfuric acid and concentrated sodium nitrite solution separately into a flask containing a thin paste of common salt and concentrated hydrochloric acid. The gases evolved are cooled and dried over calcium chloride before being led into the solution of the terpene.

Limonene also gives a nitrosochloride in high yield when heated with nitrosyl chloride in ethereal or acetic acid solution. The nitrosochloride may be obtained through the reaction of the terpene with ethyl or amyl nitrite in the presence of hydrogen chloride.¹³⁶

When pinene nitrosochloride is heated with sodium methylate, an ether oxime is obtained:¹³⁷



A nitrosochloride results through the reaction of ethylidenecyclopentane, which on heating with caustic loses the elements of hydrogen chloride forming an unsaturated oxime, hydrolysis of the latter giving Δ^1 -acetylcyclopentene,

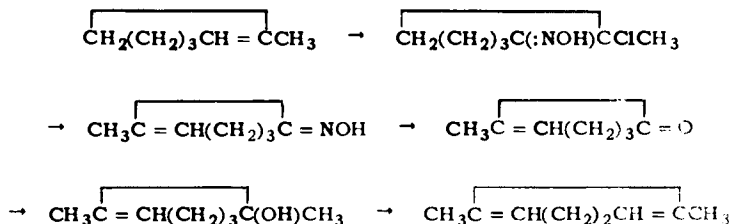


On treatment with organic bases, pinene nitrosochloride gives highly crystalline nitrolamines. Treatment with aniline under the usual conditions results in the formation of the parent hydrochloride, however, a fact which has been made use of for the preparation of pure dl- α -pinene free from β -pinene.¹³⁹ *Pinene nitrolaniline* may be obtained through the reaction of the nitrosochloride with aniline in alcoholic solution in the presence of sodium acetate.¹⁴⁰

Pinene nitrosochloride can be converted to nitrosopinene by treatment with alcoholic potassium hydroxide or, preferably, with sodium ethoxide.¹⁴¹

The monomolecular nitrosochloride of γ -terpineol has been prepared by treating an alcoholic solution of its acetate with sodium nitrite in the presence of hydrogen chloride. The nitrosobromide may be obtained in a similar manner by substituting hydrogen bromide for hydrogen chloride.

Cantharene has been obtained from the nitrosochloride of methylcyclohexene by dehydrochlorination with sodium acetate in acetic acid solution, followed by hydrolysis of the resulting oxime to the corresponding ketone, treatment of this with methylmagnesium iodide, and finally dehydrogenation of the alcohol obtained:



Reaction with Nitric and Nitrous Acids

Among the saturated cyclic hydrocarbons, cyclohexane is not acted upon by the usual nitric acid-sulfuric acid mixture, but this hydrocarbon may be nitrated by heating it in a sealed tube with dilute nitric acid.¹⁴²

On reducing nitrocyclohexane, cyclohexanone or its condensation products are obtained, apparently through the intermediate formation of cyclohexanone oxime.

Aminocyclohexane is best prepared by the reduction of the oxime of cyclohexanone in alkaline solution, or by catalytic hydrogenation in the presence of platinum catalyst.

Alkyl derivatives of cyclohexane, such as methyl or dimethyl cyclohexane, which contain a tertiary hydrogen atom, are much more readily nitrated, the nitro group replacing the tertiary hydrogen atom.

Nitrocyclohexane dissolves in alkalis, apparently forming salts of the isonitro form, a behavior which is also manifested by primary and secondary nitro derivatives of the aliphatic series.

Tertiary nitro compounds such as 1-nitrocyclohexane may be satisfactorily reduced to the corresponding oxime, since these compounds cannot isomerize to form the isonitro derivatives, and thus form oximes or ketones on reduction.

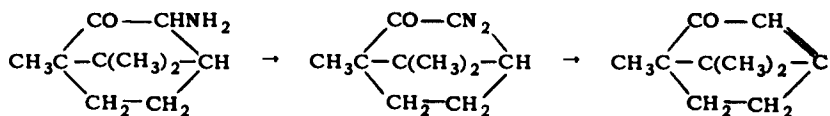
On heating fenchone with dilute nitric acid of density 1.075 at 120-130° under pressure, a mixture of secondary and tertiary nitrofenchones are formed.¹⁴³ Menthone has been converted to nitromenthone by this method; tricyclene and 4-methyltricyclene are converted to α -nitrocamphene and 4-methyl- α -nitrocamphene respectively.¹⁰¹

Camphor cannot be directly nitrated. α -Nitrocamphor can be prepared through the reduction of α -halo- α -nitrocamphor,⁵⁰⁷ which is obtained by nitrating α -halocamphor with nitric acid.⁵⁰⁸

Aminocyclohexanes yield comparatively stable nitrites when treated with nitrous acid. On heating the aqueous solutions of these compounds, decomposition takes place with difficulty, and the corresponding alcohols are formed in poor yield. Decomposition also proceeds in another direction, and results in the formation of an unsaturated hydrocarbon and ammonia.

The amino group in *D*-carvylamine sulfate may be replaced with a hydroxyl group by treatment with nitrous acid.¹⁴⁴ Fenchylamine reacts in a somewhat complicated manner with nitrous acid, giving a mixture of cineole, α -limonene, dipentene, α - and β -fenchyl alcohols, and 1- α -fenchene.¹⁴⁵

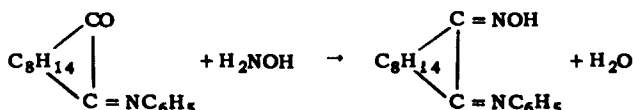
Aminocamphor reacting with nitrous acid gives diazocamphor,¹⁴⁶ which is transformed to an unsaturated ketone on heating:



Oximes of Cyclic Ketones

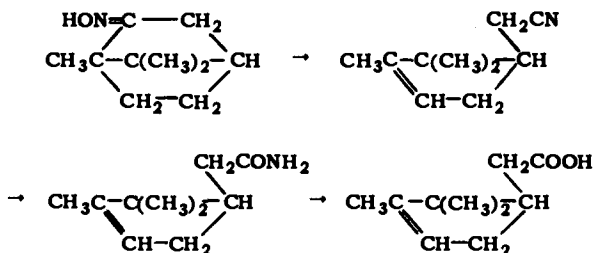
Oximes of terpenes containing the carbonyl group may be generally prepared by the usual methods. It should be noted that keto compounds with an ethylenic linkage in the α,β -position reacting with hydroxylamine yield hydroxylamino oximes.¹⁴⁷

When phenyliminocamphor is heated with hydroxylamine in alkaline solution, two stereoisomeric phenyliminocamphoroximes are obtained:¹⁴⁸

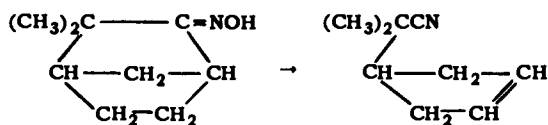


Neither α - nor α' -chlorocamphor yield oximes on treatment with hydroxylamine, but give a mixture of isomeric camphorquinone dioximes.¹⁴⁹ α -Bromocamphor shows a similar behavior. ω -Chlorocamphor gives an oxime.

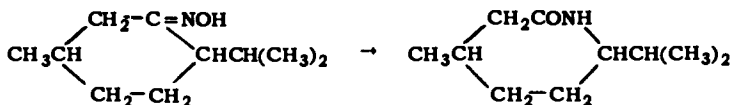
Camphoroxime, digested with mineral acids or with acid chlorides, undergoes a Beckmann transformation.¹⁵⁰ The primary product is undoubtedly *d*- α -camphenonenitrile, which is converted to the corresponding amide and finally to the acid:



On digestion of camphenilone oxime with dilute sulfuric acid, the nitrile of camphoceanic acid is formed in addition to camphenilone:¹⁵¹



When 1-menthone oxime is treated with phosphorus pentachloride in chloroform solution or with concentrated sulfuric acid, it is converted into an isoxime:¹³²



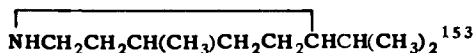
When allowed to react with an excess of phosphorus pentachloride, the isoxime undergoes ring fission and is converted into an unsaturated nitrile,



On digestion with concentrated potassium hydroxide solution at 220 to 230°, the oxime is converted to 2,6-dimethyloctane-8-carboxylic acid,

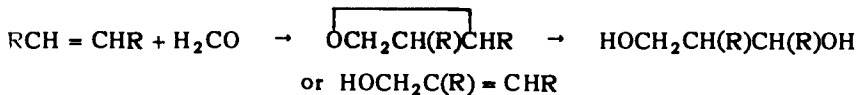


Reduced with sodium and amyl alcohol, the oxime is converted to a cyclic imine,

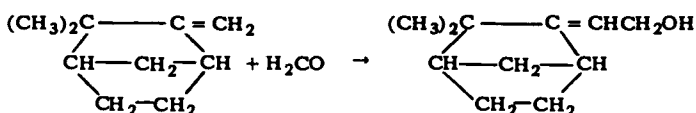


Reactions with Formaldehyde, etc.

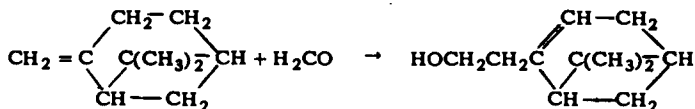
Formaldehyde is capable of reacting with certain unsaturated compounds, apparently first forming an oxide which may then hydrolyze to a glycol or may undergo rearrangement to an unsaturated alcohol:¹⁵⁴



Camphene and trioxymethylene react, when heated, to form an unsaturated alcohol:¹⁵⁵



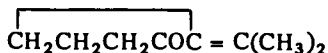
β -Pinene condenses with formaldehyde forming "nopol", an alcohol having a double bond in the ring:¹⁵⁶



Cyclopentadiene reacts with aldehydes or ketones in the presence of sodium

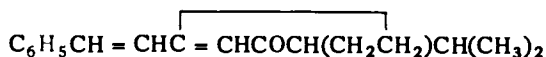
ethoxide, to form substituted fulvenes of the type $\text{CH} = \text{CHCH} = \text{CHC} = \text{CRR}'$. Cyclopentanone readily condenses with aldehydes, RCHO , to form derivatives

of the type $\text{CH}_2\text{CH}_2\text{C}(\text{:CHR})\text{COC} = \text{CHR}$.¹⁵⁷ With acetone the compound



is obtained.¹⁵⁴ The reaction of verbanone with benzaldehyde in the presence of hydrogen chloride is accompanied by ring cleavage, with the formation of a dibenzylidene derivative.

One methyl group in piperitone is reactive and capable of reacting with aldehydes, giving with benzaldehyde the compound

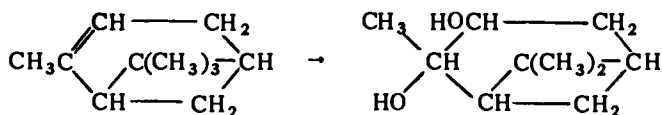


π -Formyl- π -apocamphor, allowed to remain in contact with water in the absence of oxygen, undergoes cleavage the formyl group becoming replaced by hydrogen, forming santenone.¹⁵⁸

Oxidation of Unsaturated Carbocyclic Compounds

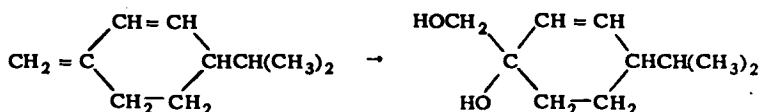
Oxidation of an unsaturated compound with potassium permanganate under mild conditions generally results in the formation of a glycol. This is the

case, for example, with α -pinene which, with neutral postassium permanganate, is converted to a dihydric alcohol:¹⁵⁹



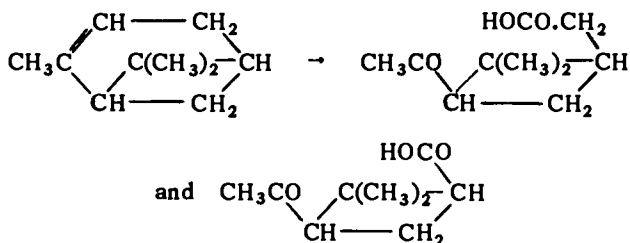
Some 1-hydroxypinocampnone is also formed in the reaction; this is oxidized very slowly under the conditions of the reaction, but is rapidly converted to pinonic acid with acid permanganate.

Oxidation of *phellandrene* with very dilute potassium permanganate at 0° also gives a glycol:¹⁶⁰



A glycol is similarly obtained from *aabinene*, together with a hydroxy acid, d-sabinenic acid, which on further oxidation with potassium permanganate gives sabina ketone. *Limonene* gives p-menthane-1,2,8,9-tetrol, further oxidation resulting in the formation of a diketo acid, $\text{CH}_3\text{COCH}_2\text{CH}_2(\text{COCH}_3)\text{CH}_2\text{COOH}$.¹⁶¹ *Terpinene-1-ol* gives at first a trihydric alcohol, but on further oxidation the latter is converted to α,δ -dihydroxy- α -methyl- δ -isopropyladipic acid. A similar reaction takes place with *terpinene-4-ol*. *Dihydrocarvone* gives a 8,9-diol, which on further oxidation with chromic acid is converted to a diketone.

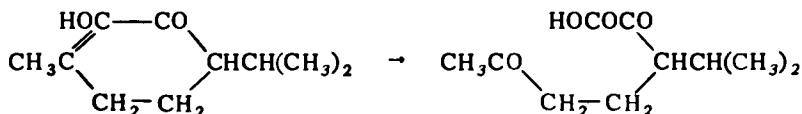
Oxidation of unsaturated carbocyclic compounds under more vigorous conditions may result in the formation of a keto acid. Thus, vigorous oxidation of α -pinene with permanganate gives pinonic and pinononic acid



Δ^3 -Carene in acetone solution gives d-1,1-dimethyl-2- γ -ketobutylcyclopropane-

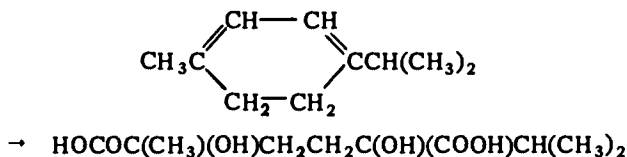
3-carboxylic acid, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2\text{CHCOOH}$, in excellent yield.

Diosphenol gives a keto dicarboxylic acid on oxidation with potassium permanganate:

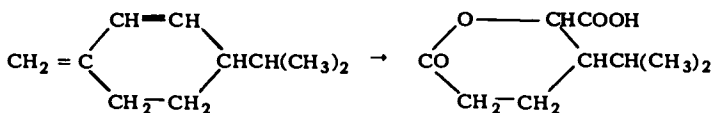


On distillation under vacuum, this acid is converted to the cyclic keto acid 2-

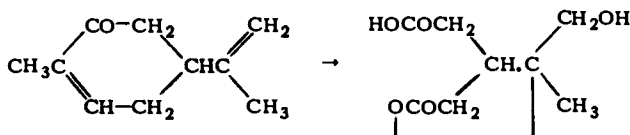
isopropyl- Δ^6 -cyclohexen-5-one-carboxylic acid. α,δ -Dihydroxy- α -methyl- δ -isopropyladipic acid results from the oxidation of α -terpinene with potassium permanganate:¹⁶²



Phellandrene is converted on vigorous oxidation with potassium permanganate to the lactone of α -hydroxy- β -isopropyladipic acid¹⁶³

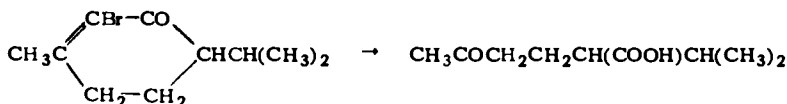


Phellandral, $(\text{CH}_3)_2\text{CHCHCH}_2\text{CH}=\text{C}(\text{CHO})\text{CH}_2\text{CH}_2$, gives an oxidation with the same reagent the dibasic acid $\text{HOCOCH}_2\text{CH}[\text{CH}(\text{CH}_3)_2]\text{CH}_2\text{CH}_2\text{COOH}$. Carvone gives hydroxy-terpenylic acid on oxidation with permanganate:¹⁶⁴

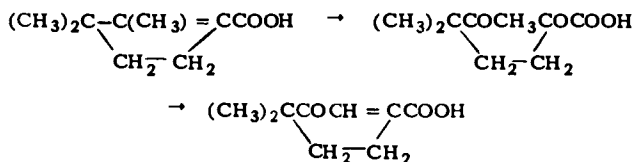


On careful oxidation with potassium permanganate *carvenone* gives a dibasic hydroxy acid, α -methyl- α' -isopropyl- α' -hydroxyadipic acid, together with α -methyl- γ -isobutyric acid and α -methylglutaric acid.

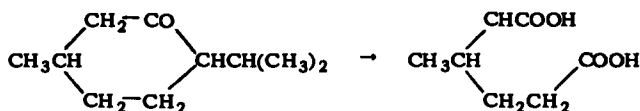
Piperitone oxidized with alkaline potassium permanganate, gives α -hydroxy- α -methyl- α' -isopropyladipic acid, γ -acetyl- α -isopropylbutyric acid, and α -isopropylglutaric acid. In neutral solution diosphenol is obtained.¹⁶⁵ Oxidized with potassium permanganate, the monobromide of piperitone gives γ -acetyl- α -isopropylbutyric acid:



Isolaunolic acid, treated with neutral, ice-cold potassium permanganate solution, is converted to a large extent to isolaunonic acid¹⁶⁶



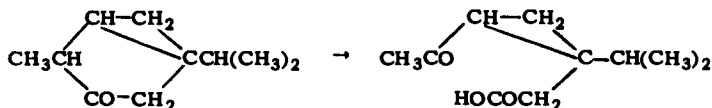
Oxidation with potassium permanganate may cause cleavage of the ring of cyclic ketones at the carbonyl group. Thus, menthone is converted principally to d - β -methyladipic acid,¹⁶⁷



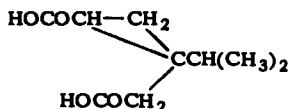
together with some β -methyl- δ -isobutyryl-*n*-valeric acid, methylsuccinic acid, etc.

The oxidation of *carvomenthone* with potassium permanganate at 40–45° results in the formation of 2-isopropylhexan-5-onecarboxylic acid, while oxidation at the boiling temperature gives isopropylsuccinic acid. The ketonic acid is also formed on oxidation of the compound with chromic acid or with hydrogen peroxide in the presence of vanadium pentoxide.¹⁶⁸

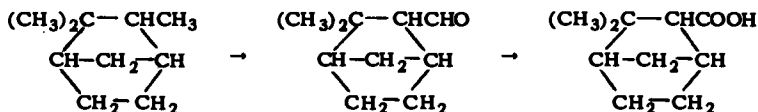
Thujone is converted on treatment with potassium permanganate to α - and β -thujaketic acids:



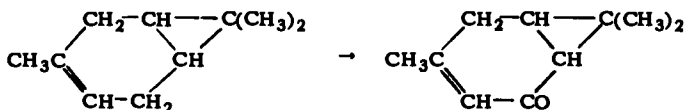
On oxidation with sodium hypobromite, this acid gives the stable *d*- α -thujadicarboxylic acid



Treatment with potassium permanganate may result in the oxidation of a methyl or methylene group. Isocamphane, for example, is converted to camphanilaldehyde, camphenilanic and isocamphenilanic acids:



Δ^3 -Carene is converted to an unsaturated ketone:



β -Thujene is remarkably resistant to the action of potassium permanganate. *Santene hydrate* and *tricyclene* are also very resistant to the action of this reagent. *1-Epicamphor* is not attacked by cold dilute potassium permanganate solution. *Fenchone* shows great stability toward oxidizing agents.

Oxidation of unsaturated compounds with *chromic acid* (*) may also result in the formation of keto acids with ring fissure. Thus, limonene oxidized with chromic acid gives a keto lactone:¹⁶⁹

(*) Many oxidations with chromic acid have been carried out with *Beckmann's mixture* which is obtained by adding five parts of concentrated sulfuric acid with stirring to a solution of six parts potassium dichromate in thirty parts of water.

1-Menthone is converted to β -methyl- δ -isobutyryl- n -valeric acid when oxidized with an acetic acid solution of chromic acid.¹⁷⁶

Δ^3 -Carene gives a mixture of d -homoterpenyl methyl ketone, 1-*trans*-crotonic acid, terpenylic acid and terebic acid on oxidation with Beckmann's chromic acid mixture.¹⁷⁷

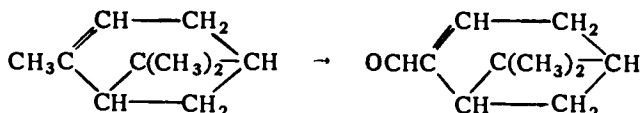
Camphor is only slowly attacked by chromic acid, but on prolonged warming, a mixture consisting essentially of camphoric acid and isocamphoric acid is obtained. 5-Ketocamphor is obtained by the chromic acid oxidation of 5-hydroxycamphor, 6-hydroxycamphor, camphor, and bornyl acetate.⁵⁰⁹ A by-product of the chromic acid-acetic acid oxidation of bornyl acetate is 6-ketocamphor,⁵¹⁰ which is hydrolyzed by acids to α -campholonic acid.⁵¹¹

Carbinol groups in cyclic hydrocarbons are converted to carbonyl groups on careful oxidation with chromic acid. Thus, 1-menthol may be converted almost quantitatively into 1-menthone.¹⁷⁸

Oxidation of *terpinene* with *chromyl chloride* results in the formation of *p*-tolylpropaldehyde and *p*-tolyl methyl ketone.¹⁷⁹ Limonene is converted by this reagent principally to cymene, which is further oxidized to α -*p*-tolylpropaldehyde and *p*-tolyl methyl ketone.¹⁸⁰

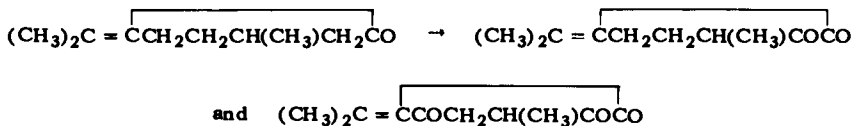
Limonene reacting with chromyl chloride in carbon disulfide solution, forms an addition compound, $C_{10}H_{16}2CrO_2Cl_2$; this is decomposed by water to a mixture of α -*p*-tolylpropaldehyde and *p*-tolyl methyl ketone.¹⁸¹

Selenium dioxide is capable of oxidizing reactive methyl or methylene groups in cyclic compounds. α -Pinene is oxidized by this reagent to myrtenal:



By using a deficiency of selenium dioxide, it is possible to isolate myrtenol, which is therefore a primary product of the oxidation. β -Pinene is oxidized by this reagent to *d*-pinocarvone.

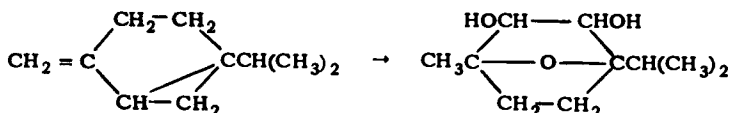
Pulegone is oxidized by selenium dioxide to a diketone and a triketone:¹⁸²



Camphor is converted by selenium dioxide in acetic acid solution to camphorquinone in good yield,¹⁸³ and *santene* is converted by a similar treatment to santoquinone.¹⁸⁴

Oxidation with *hydrogen peroxide* gives the expected glycol with Δ^3 -carene, which on treatment with sulfuric acid gives a mixture of *p*-cymene and carene oxide.¹⁸⁵ The oxide is remarkably stable and cannot be reconverted to the glycol by sulfuric acid.

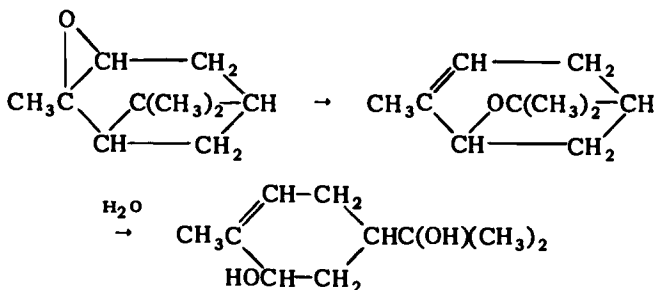
Sabinene treated with hydrogen peroxide in acetic acid solution gives isomeric glycol anhydrides:¹⁸⁶



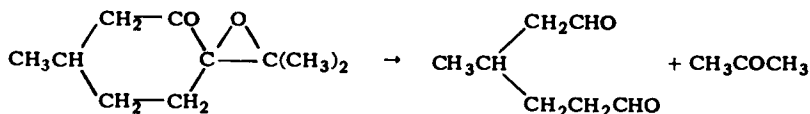
Verbenone is oxidized by alkaline hydrogen peroxide to verbenone oxide. Other cyclic ketones containing an ethylenic linkage in α, β -position with respect to the carbonyl group are also converted to the corresponding oxide on treatment with this reagent.

The oxidation of α -pinene with hydrogen peroxide proceeds in a complicated manner, hydration and molecular rearrangement proceeding simultaneously.¹⁸⁷

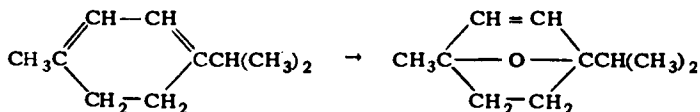
Oxidation of cyclic unsaturated compounds with *perbenzoic acid* generally results in the formation of the expected oxide. α -Pinene, for example, is converted to α -pinene oxide.¹⁸⁸ On hydration of the oxide, pinol is formed as an intermediate, and *sobrerol* as the final product



Pulegone is also converted to an oxide on treatment with *perbenzoic acid*.¹⁸⁹ When the oxide is digested with dilute sulfuric acid it gives a dialdehyde and acetone



The oxidation of *terpinene* with *perbenzoic acid* results in the formation of 1,4-oxido- Δ^2 -p-menthene:¹⁹⁰



d-Carene, treated with *perbenzoic acid*, is converted to an oxide which undergoes rearrangement to an unsaturated aldehyde under the action of sulfuric acid. *Limonene* gives with *perbenzoic acid* a monoxide and a dioxide.¹⁹¹

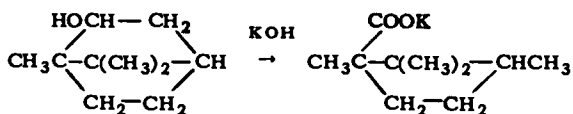
Certain cyclic compounds are *dehydrogenated* to aromatic derivatives on treatment with *ferric chloride*. *Dihydrocarvone* is converted to *carvacrol* when treated with *ferric chloride* in acetic acid solution.¹⁹² *Piperitone* is similarly converted to *thymol* in 25% yield. *Thujone* is converted to *carvacrol*, following cleavage of the cyclopropane ring.¹⁹³

Oxidation of *pinene* with *nitric acid* results in the formation of terpenylic, terebic, *p*-toluic, and terephthalic acids.¹⁹⁴ α -Terpineol gives with this reagent

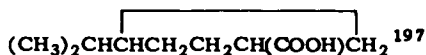
terpenylic and terebic acids; camphor is converted to the tribasic camphoric acid.

Tricyclene heated at 125-130° with dilute nitric acid gives α -nitrocamphene.¹⁹⁵

Borneol fused with potassium hydroxide at 250-280° under pressure undergoes cleavage and oxidation, giving the potassium salt of campholic acid:¹⁹⁶



A similar cleavage takes place when camphenilone is fused with potassium hydroxide, with the formation of β -dihydrocamphoceenic acid,



Camphor yields campholic and isocampholic acids. Oxidation of camphorquinone also occurs on fusion with potassium hydroxide, camphoric acid being the result of the reaction.¹⁹⁸ Pulegone is converted to 1-methylcyclohexane-3-one when heated with alkali.

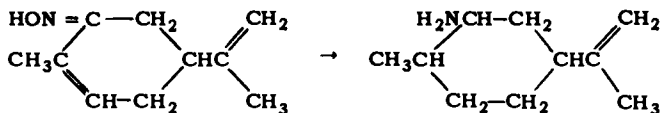
Reduction of Unsaturated Carbocyclic Compounds

The unsaturated bond in cyclic compounds may be reduced by use of sodium and alcohol. Pulegone, for example, is converted to *l*-menthol by this method.¹⁹⁹ *d*-, *l*- and *dl*-Piperitones are converted to *dl*-menthols, some *dl*- α -phellandrene being also formed.

Carone is converted by the same reagents to dihydrocarveol.²⁰⁰

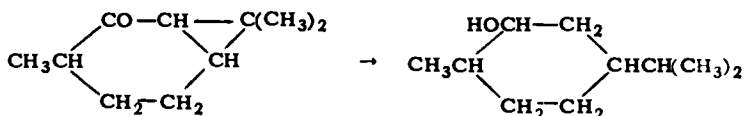
Eucarvone, $\text{CH}_3\text{C}=\text{CHCH}=\text{CHC}(\text{CH}_3)_2\text{CH}_2\text{CO}$, reduced with sodium and alcohol gives a mixture of α -dihydroeucarveol $\text{CH}_3\text{CHCH}_2\text{CH}=\text{CHC}(\text{CH}_3)_2\text{CH}_2\text{CHOH}$, and tetrahydroeucarveol.²⁰¹

Carvoximes are reduced to dihydrocarvylamine by sodium and alcohol.²⁰²



while with sodium amalgam carvylamine is obtained.²⁰³

Thujone has been converted by sodium and alcohol to thujyl alcohol.²⁰⁴ Carone, reduced with sodium and moist ether, gives carvomenthyl.²⁰⁵



d-Fenchone oxime reduced with sodium and alcohol is converted to *l*-fenchylamine.²⁰⁶ Similarly santenone oxime gives santenylamine.

α -Terpinene nitrosite reduced with the same reagents gives a mixture of carvenone, carvomenthone, and carvomenthylamine.

Carvone may be reduced in the presence of platinum black to *d*-carvotanacetone, *l*-carvomenthone, or *l*-carvomenthol at will, by the proper regulation of the supply of hydrogen.²¹⁶ Catalytic hydrogenation of *aabinene* in the presence of platinum gives *d*-thujane. *Limonene* hydrogenated in the presence of platinum black is converted to Δ^1 -*p*-menthene or *p*-menthane.²¹⁷

Reduction of unsaturated cyclic compounds has also been effected by use of nickel as a catalyst. *a*-*Terpinene* has, thus, been reduced to *p*-menthane.²¹⁸

α -Pinene reduced in the presence of nickel at 220-230° has been converted to *trans*-*f*-pinane, while *d*-*aabinol* reduced in the temperature range 170-175° is converted to a mixture of thujane and a hydrocarbon of unknown structure. *Carvone*, catalytically reduced in the presence of nickel, gives a mixture of carvomenthols.²¹⁹ At 280° under 120 atm pressure, and using a nickel oxide catalyst, carvomenthol was obtained, while at 220-240° only the ethylenic linkages were reduced, giving carvomenthone.²²⁰

The reduction of *l*-*carvone* with aluminum isopropoxide results in the formation of carveols.²²¹ Similarly *l*-*piperitone* is converted to *l*-*piperitol*.²²²

Dehydrogenation of Carbocyclic Compounds

Cyclic compounds may be dehydrogenated to the aromatic state by various methods, principally by heating with sulfur or with selenium.²²³

Dehydrogenation with Sulfur

Sulfur has been first used for the dehydrogenation of colophony and for *a*-naphthene".²²⁴

In carrying out dehydrogenation with sulfur, this element is used in the theoretically required quantity. Partial dehydrogenation may be brought about by using a deficiency of sulfur. Thus, dodecahydrochrysene may be converted to octahydrochrysene by use of the proper quantity of sulfur.²²⁵

The mixture of sulfur and the compound is usually heated in the temperature range 180-250°. A solvent is not used, as a rule, although naphthalene has been employed as a solvent in the dehydrogenation of cyclohexanone,²²⁶ and quinoline has been used in the aromatization of tetrahydrobenzpyrene.²²⁷

The dehydrogenation of *carboxylic acids* derived from tetralin and tetrahydrophenanthrene has been usually carried out under reduced pressure. This precaution avoids the loss of the carboxyl group, although decarboxylation of 1-methyltetralin-4-carboxylic acid occurs even under reduced pressure.²²⁸ A particularly rapid dehydrogenation of the anhydrides of dihydronaphthalene- and dihydrophenanthrene-*o*-dicarboxylic acids has been observed.²²⁹

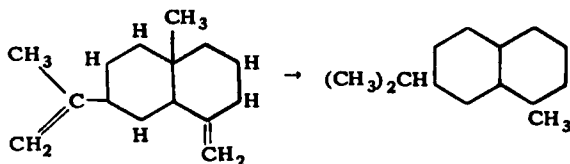
The dehydrogenation of *ketones* without secondary decomposition is more difficult than that of acids; phenol has been obtained, however, from cyclohexanone, and *a*-naphthol from *a*-tetralone.²³⁰ Esters have been successfully dehydrogenated.²³¹ Aromatic methoxyl groups are unaffected during dehydrogenation with sulfur.

All known dicyclic sesquiterpenes are converted on heating with sulphur at 200° to one of two derivatives of naphthalene, cadalene, C₁₅H₁₈, or eudalene, C₁₄H₁₆.²³² The majority of tricyclic terpenes are not dehydrogenated to naphthalene derivatives,²³³ copane forming an exception and yielding cadalene.²³⁴

As a rule, the further the compound is removed from the aromatic state, the

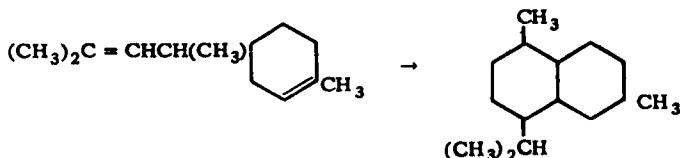
more resistant it is to the dehydrogenating action of sulfur. Thus, dihydronaphthalenes are readily dehydrogenated, while the fully hydrogenated tetrahydrocadinene could not be aromatized with sulfur.²³⁵ 1-(1'-Naphthyl)cyclohexene was readily converted to 1-phenylnaphthalene,²³⁶ while the corresponding saturated hydrocarbon was not dehydrogenated.²³⁷ 2-Cyclohexylnaphthalene has been successfully dehydrogenated to 2-phenylnaphthalene. An *infused* aromatic ring apparently facilitates dehydrogenation.²³⁸

In the dehydrogenation of selinene and eudesmol one carbon atom is eliminated from the molecule with the formation of 1-methyl-7-isopropylnaphthalene:



1,1-Dimethyltetralin is not dehydrogenated by sulfur at 221°.

The monocyclic zingiberene yields cadalene when heated with sulfur



Di-o-tolyl undergoes ring closure when heated with sulfur at 250°, giving phenanthrene.

Dehydrogenation with Selenium²²³

While dehydrogenation by use of selenium proceeds satisfactorily at a higher temperature than with sulfur, certain advantages are connected with the use of selenium. The yields, on the whole, are better, and the side reactions proceed to a lesser degree. Moreover, certain compounds, such as elemol and elemene, which are not affected by sulfur, are dehydrogenated by selenium.²³⁹

Hydroaromatic compounds containing no quaternary carbon atoms are readily aromatized, especially if the compound already contains one or more aromatic rings. Fully saturated rings are more resistant to dehydrogenation, decalin being unaffected when heated with selenium to 340-360°, although it is converted to naphthalene at 370-390°.²⁴⁰ With most fully saturated compounds, dehydrogenation with selenium begins at about 350°. The presence of an aromatic ring in the molecule facilitates dehydrogenation.²⁴¹

No migration of alkyl groups has been observed up to 350° from positions 1 to 2 in naphthalene, and 3 to 4 in phenanthrene when dehydrogenation is carried out by means of selenium, providing no neighboring substituent is eliminated in the course of the reaction.²⁴²

Derivatives of hydrindene, cyclopentane, and cyclooctane resist the action of selenium at 350°, and molecular rearrangements occur at higher temperatures.²⁴³

Fully saturated cyclic compounds containing quaternary carbon atoms also resist dehydrogenation at about 300-350°.²⁴⁴

Angular methyl groups are eliminated at customary temperatures during dehydrogenation with selenium.

Ring closure has been observed in the course of dehydrogenation with selenium at relatively high temperatures. Thus, naphthalene has been obtained from 1,2-dimethylcyclohexene at 420°. ²⁴⁵

1,1,3-Trimethyl-2-n-butylcyclohexane heated with selenium at 390-400° loses the butyl and one methyl group to become converted to m-xylene. ²⁴⁰

The spiroketone $\text{CH}_2(\text{CH}_2)_2\text{CH}_2\text{CCO}(\text{CH}_2)_3\text{CH}_2$ and the derived hydrocarbon are converted to naphthalene on heating at 280-320° with selenium. ²⁴⁶

Selenium is particularly prone to eliminate oxygen containing groups during dehydrogenation. Methoxyl groups may remain unaffected if hydrogenation is carried out below 300°. ²⁴⁷

Reduction of cyclic keto groups is observed in many instances. ²⁴⁸ The vitamin D adduct of maleic anhydride is converted to 2,3-dimethylnaphthalene on dehydration with selenium. ²⁴⁹

Esters of hydroaromatic acids have been dehydrogenated with selenium to the corresponding free aromatic acids without decarboxylation. ²⁵⁰

Catalytic Dehydrogenation

Dehydrogenation of carbocyclic compounds may be effected by heating the compound in contact with certain metals. Platinum and palladium in the finely divided condition are contact agents best suited for the purpose. The finely subdivided metals are normally prepared by reduction of their salts in aqueous solution with hydrogen, formaldehyde, or formic acid. ²⁵¹ The reduced metals may be supported on charcoal, asbestos, etc. ²⁵²

The dehydrogenating effect of platinum and other noble metals on cyclohexane and its homologs becomes appreciable at 170° and is maximal at 300°. Cyclopentane derivatives are unaffected at these temperatures, whereas other ring systems undergo alterations of the carbon skeleton.

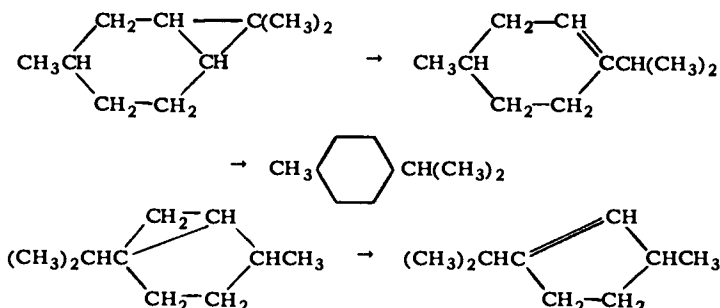
Fully reduced aromatic derivatives are readily dehydrogenated over noble metal catalysts. The behavior of partly reduced compounds, such as cyclohexene and cyclohexadiene, is more complicated. Substances of this type rapidly undergo a disproportionation at high temperatures in the presence of platinum or palladium catalysts, with the formation of a mixture of aromatic and saturated compounds. ²⁵³ $\Delta^{2,5}$ -Dihydroterephthalic ester gives a mixture of terephthalic ester and *cis* and *trans* hexahydro derivatives when heated with palladium black above 140°. Similar results have been obtained with terpenes and related compounds. Many of these changes involve the hydrogenation of extracyclic double bonds.

The catalytic dehydrogenation of the simpler compounds is carried out in the vapor phase in an atmosphere of hydrogen or an inert gas, sometimes under reduced pressure. Products of more complex structure are dehydrogenated in the liquid phase.

Compounds containing a quaternary carbon atom offer considerable resistance toward catalytic dehydrogenation, and aromatization fails to proceed in many cases. For example, 1,1-dimethylcyclohexane cannot be dehydrogenated by this method. Catalytic dehydrogenation may, however, cause the elimination of an angular methyl group. ²⁵⁴

Terpenes containing cyclopropane and cyclobutane rings undergo ring fission, giving an unsaturated isomeride, which may undergo further change. ²⁵⁵ Carane, for example,

gives paracymene, while thujane is isomerized to a cyclopentene derivative which resists dehydrogenation:



Monocyclic terpenes may be converted to the parent aromatic hydrocarbons by subjecting the terpene to successive cycles of bromination followed by dehydrobromination.²⁵⁶ Limonene is converted to *p*-cymene by this treatment, while carvestrene gives *m*-cymene.

Dehydrogenation of steroids usually gives a difficultly separable mixture of several higher aromatic hydrocarbons, and the nature of the mixture can vary with the temperature of the reaction. Aromatization of an alkylated five ring system often occurs when alkylhydrindenes are heated with selenium or with palladized charcoal at 450°. ³¹⁷ Indenes, similarly treated at 350°, are partly destroyed and partly converted to hydrindenes. ³¹⁸ A hydrogenating and isomerizing action is observed with cholesterol, which is converted at 230° in part to cholestanone and cholestenone. Compounds having cyclohexane rings containing tertiary bound groups are sometimes resistant to aromatization by selenium at 360°. ³¹⁹ Dehydrogenation of cholesteryl chloride with selenium at 240-310° gave two hydrocarbons C₂₅H₂₄ and C₁₈H₁₆. ³²⁰

Cyclization of Open Chain Hydrocarbons

Cyclization of numerous hydrocarbons at 465° in the presence of chromium trioxide at atmospheric pressure has been investigated. ³²¹ Compounds the structure of which permitted the formation of six-membered rings "aromatized" to a marked degree. On the other hand, if the structure was such that six-membered ring could not form failed to aromatize to any appreciable degree.

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PART II

CARBOCYCLIC COMPOUNDS

SECTION 2. AROMATIC COMPOUNDS

CHAPTER 22

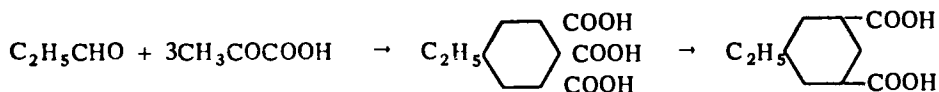
AROMATIC HYDROCARBONS

Formation

Benzene, some of its homologs, and numerous other aromatic hydrocarbons are present in coal tar, and many are recovered from this source in large quantities.

Benzene and many of its derivatives may be synthesized by a variety of reactions. Benzene is formed through the polymerization of acetylene at high temperatures. Homologs of benzene may be obtained through the polymerization of alkylacetylenes. Bromoacetylene condenses to a benzene derivative more readily than acetylene.

Acetone may be condensed to mesitylene under the influence of sulfuric acid. Similarly, formylacetic ester polymerizes to trimesinic ester. The condensation of aldehydes with pyruvic acid represents a similar reaction:



The formation of homologs of salicylic acid by intramolecular condensation of alkylidenemalononic esters in the presence of sodium ethoxide may also be mentioned.

Benzene derivatives may be obtained through the "aromatization" of alicyclic compounds containing a six-carbon ring. Preparation of such compounds has been considered in the preceding chapter. Aromatization is brought about by dehydrogenation by various methods.

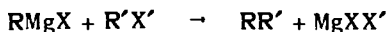
Alkyl or other organic groups may be introduced into the aromatic ring by various methods. In the *Wurtz-Fittig reaction*¹ metallic sodium is made to react with a mixture of an aromatic and aliphatic halide:



The finely shaven metal is added to the cold solution of the two halides in an indifferent solvent. The reaction, once under way, proceeds with evolution of heat, and it may be necessary to apply external cooling. Ether is the usual solvent, although petroleum ether, benzene, etc., are also employed occasionally. The reaction may be accelerated by the addition of a little acetic ester. Heating may be necessary in some cases. The reaction proceeds most readily with high molecular, normal primary alkyl halides, such as octyl and cetyl iodides.² The first stage of the reaction would appear to be the formation of sodio aryls and alkyls, followed by release of free organic residues and their final combination.³

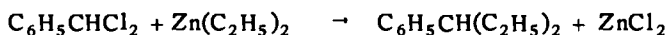
This method has been employed for the preparation of a very great number of benzene homologs. It presents the advantage that the expected compound is obtained unmixed with its isomers, and may therefore be readily obtained in the pure form.

Houben's method,⁴ which is similar to the Wurtz-Fittig synthesis, employs the aryl and alkyl halomagnesium compounds in ligroin or cyclohexane solution:



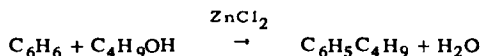
Benzene and other aromatic hydrocarbons have been alkylated also by reaction with unsaturated aliphatic hydrocarbons in the presence of a fine suspension of phosphorus pentoxide.²⁰³ The suspension is produced by mixing the pentoxide with lampblack and forming a paste with cresol. The reaction is carried out under a pressure of approximately 40 atmospheres, and in the temperature range 150 to 250°. Mono and higher substituted homologs are generally formed simultaneously.

Certain homologs of benzene have been prepared through the reaction of zinc alkyls with benzal chloride:⁵



One of the most fruitful methods for the preparation of homologs of benzene and other aromatic compounds is offered by *Friedel-Crafts synthesis*. Homologs may be obtained directly by use of alkyl halides in this synthesis. Keto compounds resulting from the reaction of acyl halides or acid anhydrides may be converted to the corresponding hydrogenated compounds by the Clemmenson method.

Benzene may be alkylated also by heating with an alcohol and zinc chloride at 260-300°.⁶

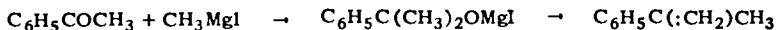


Alkylation by use of alcohols may also be accomplished in some instances by heating a mixture of the aromatic compound and the alcohol with sulfuric acid.⁷

Benzene derivatives with an *olefinic side chain* may be prepared by the usual methods employed for the preparation of olefins.

One of the most convenient methods for the preparation of aromatic olefinic compounds in which the double bond is adjacent to the ring consists in the dehydration of secondary and tertiary phenyl alkyl carbinols. The latter are obtained from acyl benzenes by reduction. Aromatic derivatives with an olefinic side chain also result through the dehydration of primary aromatic alcohols with potassium carbonate or potassium hydroxide.

The reaction products of acyl benzenes or esters of aromatic carboxylic acids with alkyl magnesium halides give aryl olefins on heating with an excess of the Grignard reagent:⁸



Olefin formation takes place also on treating the Grignard complex with dilute sulfuric acid or ammonia.

Benzene hydrocarbons with side-chains containing at least two carbon atoms may be dehydrogenated catalytically at 650 to 700°.

Benzene derivatives with *acetylenic side chains* may be prepared by the general methods employed for the preparation of substituted acetylenes.

Phenylacetylene is obtained on heating α - or ω -bromostyrene with alcoholic potassium hydroxide.⁹ This compound results also when acetophenone chloride or styrene dibromide is heated at 130° with alcoholic potassium hydroxide. Decarboxylation of phenylpropionic acid to phenylacetylene is accomplished by heating with water at 120°, or by distilling the barium or aniline salt of the acid.¹⁰

Diphenyl, Diphenylmethane and other Di- and Polyphenyl Alkyls

Diphenyl may be obtained from bromobenzene by the Wurtz-Fittig synthesis:¹¹



More highly condensed hydrocarbons are also formed in this reaction.

Diphenyl results in better yield when iodobenzene is heated at 230° with copper powder.¹² This is representative of a general method known as the *Ullman's reaction*. It is of general applicability, and is of considerable value for the synthesis of substituted diphenyls. The order of reactivity of halogens is $\text{I} > \text{Br} > \text{Cl}$. As a general rule, the bromo and chloro compounds undergo the reaction only when activating groups are present. Certain negative groups in the *ortho* or *para* position with respect to the halogen induce activation. The activating effect is greatest when the group is in *ortho* position, and least when in the *meta* position. Nitro groups are the most effective among substituents; carboxyl and carbonyl groups also cause a marked activation of the halogen. Large substituents occupying the two *ortho* positions about the halogen hinder the reaction through the steric effect.

The *procedure* is to heat the halide in an open vessel, and to add the copper powder gradually. The optimum temperature varies in the range 100 to 360° depending on the halide employed. The halide need not be subjected to special purification. The metal is generally used in threefold excess. The reaction may be carried out in diluents, such as nitrobenzene, toluene, naphthalene, *p*-cymene, biphenyl, and anthracene.

Commercial copper "bronze" is generally satisfactory for the purpose; it may be activated by treatment with iodine in acetone solution, then washing successively with hydrochloric acid and acetone. An active form of copper powder is commercially available.

o-Terphenyl has been synthesized by this method from iodobenzene and 2-iodobiphenyl. The reaction is applicable to compounds containing amino, amido, sulfamido, carboxyl and hydroxyl groups. It is necessary, however, to block such groups in order to avoid side reaction involving these groups and a second halide molecule. The amino groups may be protected by acylation or alkylation, carboxyl groups by esterification, and hydroxyl groups by etherification. The reaction has been utilized for the preparation of diphenyl aldehydes from halo benzaldehydes, the aldehyde group being protected by conversion into an azomethine.

Ullman's reaction has been employed also for the preparation of many fused

ring polynuclear aromatic compounds. Biphenylene has been obtained, for example, from 2,2'-dihalobiphenyls, and 2,7-dimethoxy-9,10-dihydrophenanthrene and 2,3,6,7-tetramethoxy-9,10-dihydroxyphenanthrene have been prepared from the appropriate diiododibenzyl derivatives. Perylene has been obtained from 1,8-diiododinanthalene.

Certain benzene derivatives, such as phenols, undergo condensation to diphenyl derivatives when heated to a high temperature:



With the simpler phenols, reaction takes place only on heating with fused alkalis.¹³ The more highly substituted phenols, such as thymol, undergo the condensation under the influence of very mild reducing agents.¹⁴ Such agents also cause the condensation of hydroquinone.

Diphenyl results from phenylmagnesium halides by the action of cupric salts.

Zincke's method, involving the reaction of an organic halide with an aromatic hydrocarbon and metallic zinc, has been utilized for the preparation of certain diphenyl derivatives.¹⁵

The most important method for the preparation of diphenyl derivatives is based on the reaction of diazo salts with aromatic compounds:¹⁶

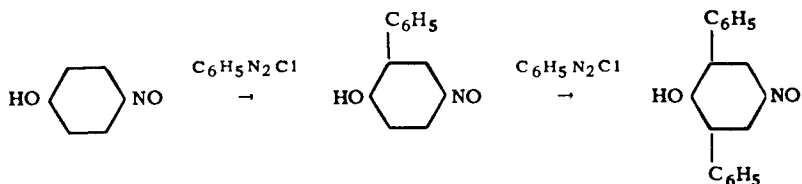


The reaction may be carried out by suspending the diazo salt in the liquid aromatic compound and adding aluminum chloride, or stannous chloride.

An alternative method is to add a 15 to 40% aqueous sodium hydroxide solution to a well-agitated mixture of the diazonium salt and the aromatic liquid maintained at 5 to 10°, until a slight excess of alkali is present. The diazo hydroxide formed during the addition of the caustic dissolves in the aromatic liquid, and the reaction proceeds with evolution of nitrogen. Another procedure is to add the diazonium salt to two equivalents of sodium hydroxide solution at 5 to 10°, and to mix and agitate the resulting sodium diazotate with the aromatic liquid at the same temperature.

By-products are formed during the reaction, among them linear polyaryls. Reduction takes place, and the diazo group is replaced by hydrogen, and some azo compounds are formed. A considerable amount of high boiling product is also found in the reaction product. The yield of diaryls is often low.

Reaction between diazo salts and *p*-nitrosophenol takes place quite readily, and two aryl groups enter the molecule:¹⁷

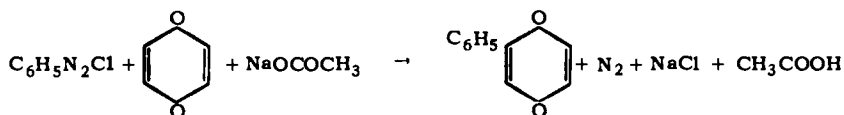


A limitation of the method is that the aromatic compound employed must be a liquid at the temperature at which the reaction is carried out, since no suitable solvents have been found that are inert toward the diazo compound or toward the intermediates formed in the reaction.

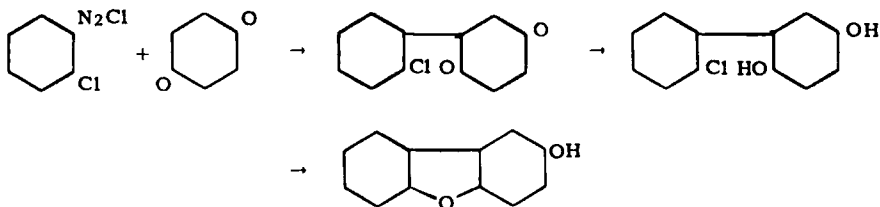
It is not possible to prepare biaryls containing free carboxyl groups directly by this method. Thus, no coupling takes place between benzene and diazotized anthranilic acid under the conditions of the reaction, although diazotized methyl anthranilate undergoes the reaction normally with benzene to form 2-carbo-methoxybiphenyl in 24% yield. Arylnaphthalenes and arylpyridines can also be prepared by this method.

Pschorr's synthesis involves the internal coupling of two aromatic nuclei through the elimination of a diazo group from one.

Aryldiazonium salts react with quinones in the presence of sodium acetate to form arylquinones.²⁰⁴ The reaction proceeds readily when the solid diazonium salt is added to a solution of the quinone in alcohol containing an excess of sodium acetate:



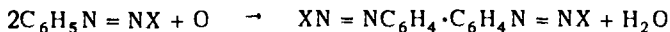
A second phenyl group may be made to enter the molecule of the quinone to form 2,5-diphenylquinone. 1,4-Naphthoquinone reacts readily only with reactive diazonium compounds. The reaction is the basis for the technical production of 3-hydroxydibenzfuran, starting from benzoquinone and o-chlorodiazobenzene:



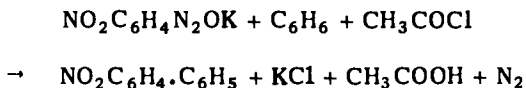
Non-quinoidal 1,2- open-chain or cyclic compounds are also arylated by diazo compounds.²¹⁵ The reaction is carried out in acetone in the presence of a cupric salt, usually cupric chloride. An acetate buffer is also used. The process is known as the *Meerwein reaction*. Only diazonium chlorides and bromides are effective; sulfates and nitrates fail to react.²¹⁶ Crotonic acid is arylated at position 2, while dienes are substituted at position 1.²¹⁷

Diazobenzene sulfate, heated with copper powder or zinc dust, is converted to diphenyl.¹⁸ Transformation into diphenyl takes place at room temperature upon the addition of copper powder to a concentrated solution of diazobenzene sulfate in concentrated acetic acid.¹⁹ An important technical application of the reaction is the preparation of anthranthrone by the internal condensation of 1,1'-dinaphthyl-8,8'-dicarboxylic acid obtained from 1-diazonaphthalene-8-carboxylic acid.

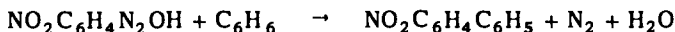
Diphenyl derivatives result on oxidation of diazo compounds with magnesium dioxide or by an electric current:



Alkaline isodiazo compounds react with aromatic compounds in the presence of acid chlorides to form diphenyl derivatives.²⁰



The free isodiazobenzohydrate reacts in the cold with aromatic hydrocarbons to form diphenyl derivatives:²¹



Gomberg and his coworkers introduced an important improvement in the method by diazotizing the amine in the smallest possible amount of water, mixing the diazo solution with the aromatic compound, and adding cold concentrated caustic to the mixture with vigorous agitation.²¹⁸ The diaryls are isolated from the non-aqueous layer by fractional distillation. The method in this modified form is known as the *Gomberg reaction*. The caustic may sometimes be replaced to advantage with sodium acetate.²¹⁹

Union of aromatic radicals with pyridine proceeds poorly by this method.²²⁰ Mixed *p*-nitrophenylpyridines are formed in 70% yield, however, when *p*-nitrodiazobenzene is made to react at 40° with an excess of pyridine.²²¹ The three isomers may be resolved in the form of their picrate.

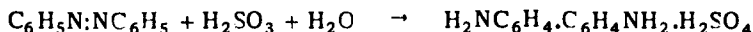
Unsym-diaryls have been prepared by mixing an aromatic compound with a triazine obtained from an aromatic diazo compound and dimethylamine and adding hydrochloric acid.²²² The yields are often good.

Diaryls are formed also through the decomposition of aromatic diazo compounds under the action of reducing agents.²²³ Diphenyl has been obtained in 50% yield by the action of copper powder on benzenediazonium sulfate in suspension in acetic anhydride.²²⁴ Diphenic acid and diphenyl-2,2'-dicarboxylic acid have been obtained in 90% yield by this method.²²⁵ 1,1'-Dinaphthyl-8,8'-dicarboxylic acid is prepared on the technical scale from 1-diazonaphthalene-8-carboxylic acid.²²⁶ Diazonaphthalene-8-sulfonic acid does not undergo the reaction, but gives instead 1,1'-azonaphthalene-8,8'-disulfonic acid. 4,8-Dinitronaphthalene-1-diazonium sulfate also behaves anomalously and gives 4,8,4',8'-tetranitro-1,1'-dinaphthylamine, but 8,8'-dinitro-1,1'-dinaphthyl is formed when 8-nitronaphthalene-1-diazonium sulfate is treated with a neutral suspension of cuprous oxide.²²⁷ Asymmetric diaryls have been prepared by this method.

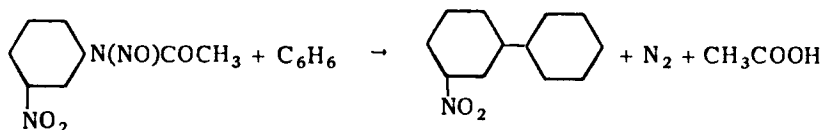
A simple procedure was employed by Oddo and Curatolo²²⁸ who diazotized the mixture of aniline and *p*-toluidine and dropped the solution of the diazo compound into an alcoholic solution of sodium ethoxide.

Junction between aryl groups occurs at positions ortho to substituents present in the aromatic nucleus.

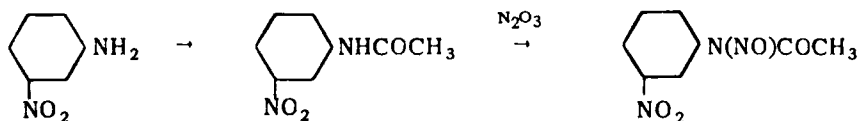
An important method of preparation of diphenyl derivatives involves the conversion of hydrazobenzene and related compounds to diaminodiphenyls by the action of acids. Thus, benzidine sulfate results from azobenzene or azoxybenzene by treatment with sulfurous acid and alcohol:²²



Combination of two aromatic groups may be brought about through the interaction of an aromatic compound with an aromatic nitrosoacetylamine:²⁰⁵

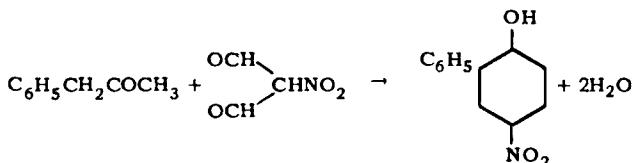


This method gives yields ranging from 40 to 70%, in contrast to yields of 15 to 35% obtained by the diazo method. The nitrosoacetylamine may be made from the amine by passing nitrous fumes, consisting of a mixture of nitric oxide and nitrogen peroxide, into an ice-cold solution or suspension of the amine in a mixture of acetic acid and acetic anhydride:



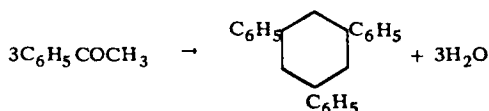
The compound can also be prepared through the reaction of nitrosyl chloride with the acetylated amine in acetic acid solution in the presence of sodium acetate. The nitroso compound is precipitated by pouring the solution into ice water and is separated by filtration.

Diphenyl derivatives have been obtained by ring closure from open chain compounds. 2-Hydroxy-5-nitrodiphenyl has been obtained through the condensation of nitromalonic aldehyde and benzyl methyl ketone in weakly alkaline solution:²³

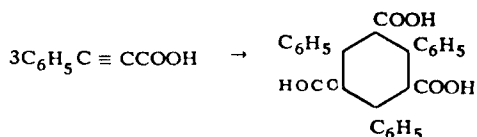


3,5-Diphenyldicarboxylic acid has been similarly obtained through the condensation of benzaldehyde and pyrotartaric acid.²⁴

sym-Triphenylbenzene results, together with some diphenyl, when acetophenone is boiled for a long period:²⁵



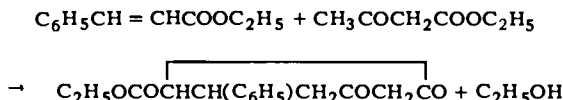
Triphenylmesitic acid is obtained when the anhydride of phenylpropionic acid is heated with aqueous potassium hydroxide:²⁶



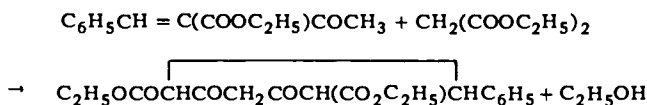
Phenylated alicyclic compounds have been obtained by various methods of

condensation. These compounds can be converted to aromatic derivatives by standard methods.

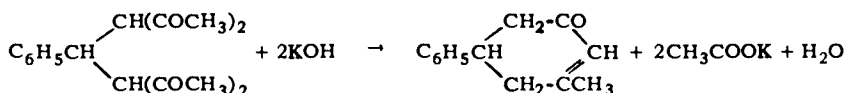
Phenyldiketocyclohexanecarboxylic ethyl ester results through the condensation of cinnamic acid with acetoacetic ester;²⁷



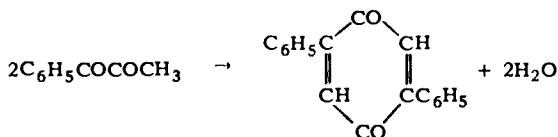
A dicarboxylic ester results through the condensation of benzylideneacetoacetic ester and malonic ester;²⁸



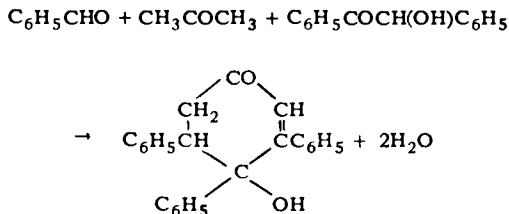
Benzylidenebisacetylacetone, heated with aqueous potassium hydroxide, gives 1-methyl-3-phenylcyclohexen-(6)-on-(5):²⁹



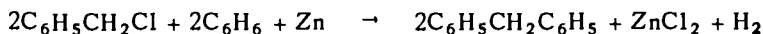
p-Diphenylquinone results when aqueous sodium hydroxide is added to acetylbenzoyl, preferably together with potassium ferricyanide;³⁰



A V-triphenyl keto cyclohexene alcohol results on heating a mixture of acetone, benzoin, and alcohol with some potassium cyanide and water.³¹ Benzaldehyde resulting from the partial breakdown of the benzoin apparently takes part in the reaction:



Diphenylmethane, $(\text{C}_6\text{H}_5)_2\text{CH}_2$, has been obtained from benzyl chloride and benzene by Zincke's reaction, i.e., by heating with zinc dust or zinc filings:³²



The reaction, which is applicable also to homologs of benzene, is not a satisfactory preparative method, since the yields are not good because of the reducing effect of metallic zinc on the chlorides. The benzyl group enters the *para* or

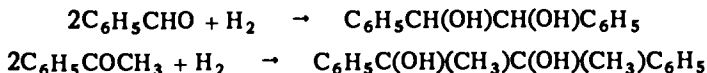
ortho position with respect to a side chain or other substituent present in the molecule.³³

The most important method for the preparation of diphenylmethane and its derivatives is that of Friedel-Crafts. The reaction proceeds at lower temperatures than Zinckes reaction and yields are much higher.³⁴

Diphenylmethane and its derivatives may also be obtained through the condensation of benzene or its homologs with formaldehyde or methylene diacetate under the action of sulfuric acid;³⁵ further, by heating a mixture of benzylbenzene sulfonate with benzene or its homologs.³⁶

Triphenylmethane may be prepared through the reaction of benzal chloride with mercury diphenyl,³⁷ or by the action of zinc dust or aluminum chloride on a mixture of benzene and benzal chloride or benzotrichloride.³⁸ It may also be obtained from carbon tetrachloride and benzene by Friedel-Crafts method,³⁹ or through the reaction of benzal chloride with phenylmagnesium bromide.⁴⁰ The compound gives a potassium salt $(C_6H_5)_3CK$ when heated with the metal; the salt reacts with carbon dioxide to form potassium triphenylacetate.

sym-Diphenylethane is obtained by the action of sodium, magnesium or copper on benzyl chloride;⁴¹ also from ethylene chloride and benzene by Friedel-Crafts reaction;⁴² through the reaction of benzene and acetylene in concentrated sulfuric acid in the presence of mercury salts;⁴³ and by the oxidation of toluene with potassium persulfate.⁴⁴ Heated with sodium hypochlorite, *p*-nitrotoluene-sulfonic acid gives 4,4'-dinitrobenzyl-2,2'-disulfonic acid, or 4,4'-dinitrostilbene-2,2'-disulfonic acid. Diphenylethane may be obtained also by reduction of its oxygenated derivatives, such as benzoin and benzil, and of unsaturated compounds stilbene and tolane. It may be pointed out that aromatic carbonyl compounds of the type of benzaldehyde and acetophenone may be converted to pinacones under the action of nascent hydrogen:

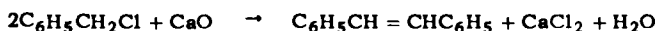


These compounds may be converted readily to diphenylethanes by reduction.

The synthesis of hexestrol, $(p)HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OH(p)$, has been effected in 36% overall yield by the action of phenylmagnesium bromide on anethole hydrobromide, $(p)CH_3OC_6H_4CHBrCH_2CH_3$, in solution in a mixture of ether and toluene and in the presence of 0.05 molal equivalent of cobalt chloride. The dimethyl ether of hexestrol which forms in the reaction is converted to hexestrol by decomposition with hydriodic acid.²²⁹

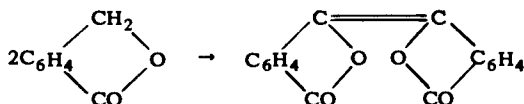
o-Chlorobenzal chloride, $ClC_6H_4CHCl_2$, treated with copper powder, gives *o*-dichlorostilbene. Benzal chloride yields stilbene by treatment with metallic silver.

Stilbene results when benzyl chloride is heated with lime:⁴⁵

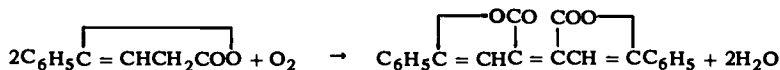


Cyano- and nitrostilbenes may also be obtained by treatment of cyano and nitrobenzene chlorides with alcoholic caustic.

Phthalid undergoes oxidation on heating to diphtalyl, which may be considered a derivative of stilbene.⁴⁶

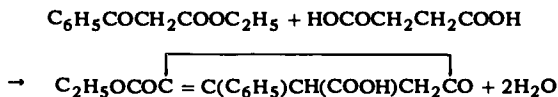


Examples of the preparation of longer alkyl chains with phenyl groups at the ends are afforded by the preparation of dibenzylacetone, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$ from the dibenzyl derivative of acetonedicarboxylic ester by decarboxylation of the free acid,⁴⁷ and of hydrocinnamoin, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}(\text{OH})\text{CH}(\text{OH})\text{CH}=\text{CHC}_6\text{H}_5$, through the reduction of cinnamic aldehyde with zinc dust.⁴⁸ The lactone of β -hydroxybenzylidenepropionic acid treated with iron chloride gives a diphenylhexane derivative:⁴⁹



Dibenzylideneacetone, $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}=\text{CHC}_6\text{H}_5$, may be obtained through the condensation of benzaldehyde with acetone.⁵⁰ Phenacyl bromide, $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$, reacting with malonic ester in the presence of sodium ethoxide, gives diphenacylmalonic ester, $(\text{C}_6\text{H}_5\text{OOCH}_2)_2\text{C}(\text{COOC}_2\text{H}_5)_2$.⁵¹

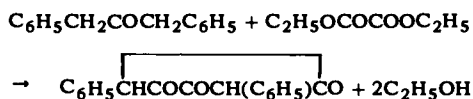
Phenylpentamethylene derivatives have been prepared through ring formation by various condensation reactions. Thus, the condensation of ethyl benzoylacetate with succinic acid results in the formation of carbethoxyphenylthion acid:⁵²



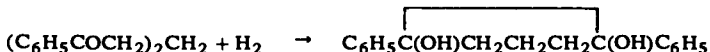
Benzil and acetone condense to form a diphenylcyclopentenone derivative:⁵³



Dibenzyl ketone and oxalic ester yield a diphenyltriketopentamethylene.⁵⁴



1-Phenyl-3,4-diketopentamethylene-2,5-dicarboxylic ester results through the condensation of β -phenylglutaric and oxalic esters.⁵⁵ 1,2-Diphenyl-1,2-dihydropentamethylene results from 1,3-dibenzoylpropane by reduction:⁵⁶



Similarly benzylidenediacetophenone, $\text{C}_6\text{H}_5\text{CH}(\text{CH}_2\text{COC}_6\text{H}_5)_2$, gives on reduction a glycol which yields 1,2,4-triphenylpentamethylene when treated with phosphorus and hydrogen iodide.⁵⁷ Tetraphenylcyclopentane results similarly from dibenzoyldiphenylpropane, $\text{C}_6\text{H}_5\text{COCH}(\text{C}_6\text{H}_5)\text{CH}_2\text{CH}_2\text{CH}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_5$.⁵⁸

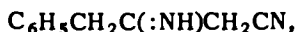
Fused-Ring Polynuclear Aromatic Compounds

Naphthalene results when a mixture of benzene and acetylene is passed through a red-hot tube.⁵⁹ Phenylbutylene, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, cyclizes to naphthalene when its vapors are passed over red-hot lime; phenylbutylene dibromide also gives naphthalene when similarly treated.⁶⁰ α -Divinylbenzene,

which may be obtained from *o*-diethylbenzene, may be further dehydrogenated quantitatively to naphthalene. Benzylidenepropionic acid,



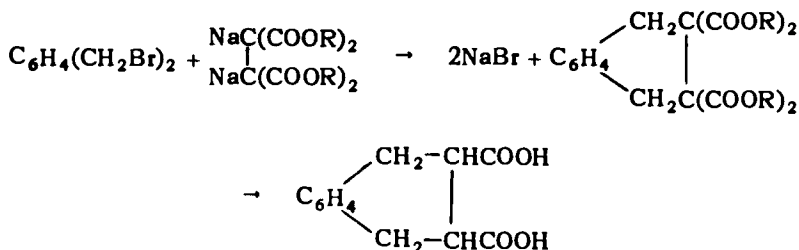
is cyclized on heating to α -naphthol;⁶¹ other unsaturated acids of the same type have been cyclized to naphthalene derivatives.²³⁰ The cyclization of benzylallylacetic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{COOH})\text{CH}_2\text{CH}=\text{CH}_2$, gives tetrahydromethylnaphthalenecarboxylic acid.⁶² Styrenepyruvic acid, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{COCO}_2\text{H}$, cyclizes to 1-naphthoic acid.⁶³ 2-Phenyl-1,3-dihydroxynaphthalene is formed when α - γ -diphenylacetoacetic ester is heated with concentrated sulfuric acid.²³¹ Phenylacetylamlonic ester, $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}(\text{COOR})_2$, treated in the same manner gives naphthoresorcincarcboxylic ester.²³² γ -Phenyl- β -iminobutyronitrile,



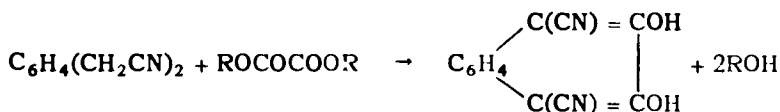
condenses under the action of concentrated sulfuric acid to 1,3-diaminonaphthalene;⁶⁴ certain other iminonitriles, such as $\text{CH}_3\text{C}_6\text{H}_4\text{C}(:\text{NH})\text{CH}(\text{CN})\text{C}_6\text{H}_5$, and $\text{CH}_3\text{C}_6\text{H}_4\text{C}(:\text{NH})\text{CH}(\text{CN})\text{COOR}$, also condense to naphthalene derivatives.⁶⁵ Phenylglycol, $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}_2\text{OH}$, condensing with itself in the presence of dilute sulfuric acid, gives 2-phenylnaphthalene,⁶⁶ while the self-condensation of phenylpropionic acid, $\text{C}_6\text{H}_5\text{C}\equiv\text{CCOOH}$, in the presence of acetic anhydride or phosphorus oxychloride gives 1-phenylnaphthalene-2,3-dicarboxylic anhydride.

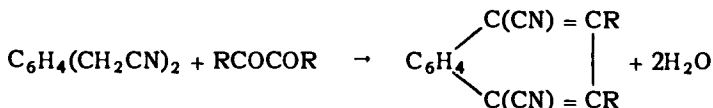
Aniline condenses with pyromucic acid, $\text{HOOC}=\text{CHCH}=\text{CHO}$, when a mixture of the two compounds is heated to 300° with zinc chloride forming α -naphthylamine.⁶⁷ Phenylbutyryl chloride, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{COCl}$, subjected to the Friedel-Crafts synthesis, gives ketotetrahydronaphthalene.⁶⁸

o-Xylylene bromide, reacting with the sodio derivative of ethane tetracarboxylic ester, gives tetrahydronaphthalenetetracarboxylic ester which, on hydrolysis, gives tetrahydronaphthalenedicarboxylic acid:⁶⁹

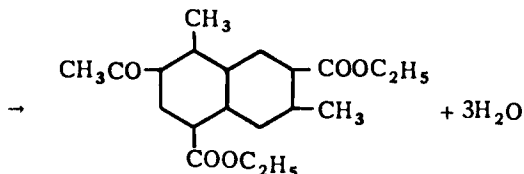


o-Xylylene cyanide, reacting with ethyl oxalate or with α -diketones in the presence of sodium ethoxide, gives naphthalene derivatives:⁷⁰

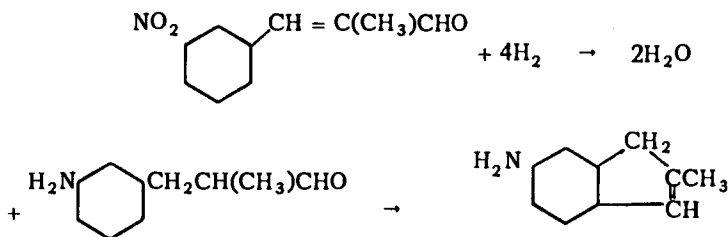




α,γ -Diacetocrotonic ester, condensing with itself in the presence of metallic sodium, gives aceto-1,6-dimethylnaphthalenedicarboxylic ester, which can be easily converted to 1,6-dimethylnaphthalene:⁷¹

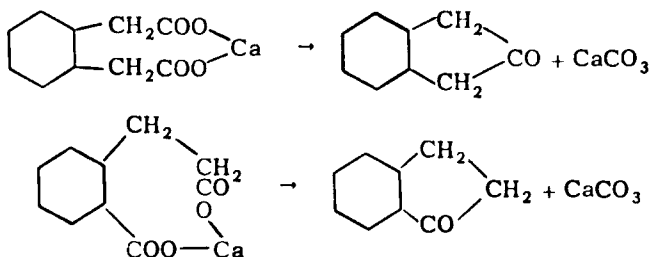


Indenes result through the cyclization of aldehydes of the cinnamic series. Thus, the reduction of *m*-nitro- α -methylcinnamaldehyde with zinc and hydrochloric acid results in the formation of 2-methyl-6-aminoindene:⁷²

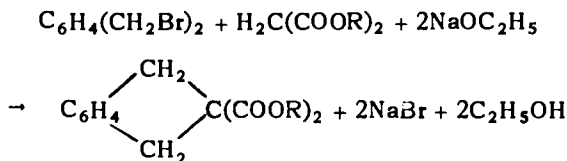


Ketones of the hydrocinnamic series, such as $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COCH}_3$, undergo cyclization more readily than the corresponding aldehydes,⁷³ while derivatives of hydrocinnamic acid cyclize more readily than the ketones.⁷⁴ Substituted cinnamic acids treated with hot sulfuric acid, or phosphorus pentoxide, give indone derivatives.⁷⁵ Halogen and nitro substituted alkylated hydrocinnamic acids, whether alkylated in the nucleus or the side chain, give dihydroindone derivatives. Cinnamic acid and hydrocinnamic acid react in the same manner as the corresponding aldehydes.⁷⁶

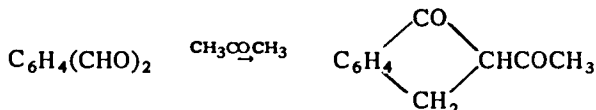
Hydrindones are formed on distillation of salts of *o*-phenylene and hydrocinnamic *o*-carboxylic acids:⁷⁷



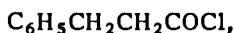
Hydrindones are obtained through the reaction of *o*-xylylene halides with malonic esters in the presence of sodium ethoxide:⁷⁸



Phthalic dialdehyde reacting in alkaline solution with methyl ketones and methyl keto carboxylic acids gives hydrindone derivatives:⁷⁹

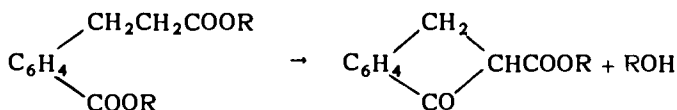


Hydrindone results in good yield from hydrocinnamyl chloride,

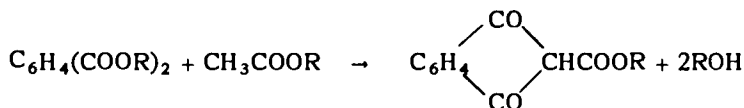


by Friedel-Crafts reaction.⁸⁰

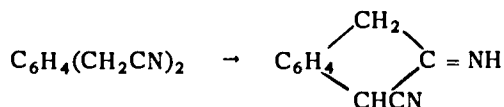
Indene derivatives may be obtained by ester condensation. Thus, hydrocinnamic *o*-carboxylic ester yields a hydrindonecarboxylic ester on condensation under the action of sodium or sodium ethoxide:



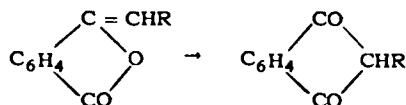
1,3-Diketohydrindenes are formed through the reaction of diethyl phthalate and aliphatic esters or ketones:⁸¹



The *Thorpe reaction* has been utilized for the synthesis of hydrindone derivatives. Thus, 1-cyano-2-iminohydrindene has been obtained through the condensation of *o*-phenylenediacetonitrile under the action of sodium ethoxide:⁸²

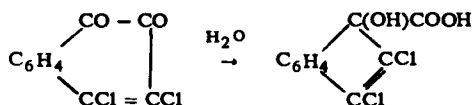


Phthalides are converted under the action of sodium ethoxide into the sodium compound of isomeric diketohydrindenes:⁸³

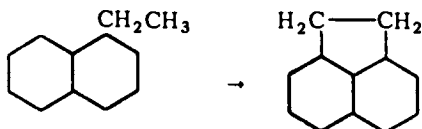


Certain chlorinated naphthols, naphthoquinones, aminonaphthols, etc. undergo molecular rearrangement to indene derivatives. Intermediate compounds containing the

groupings --COCO-- or $\text{--COCCl}_2\text{--}$ are apparently formed and undergo fission before being transformed to indene derivatives:⁸⁴



Acenaphthene is formed by the self-condensation of 1-ethylnaphthalene at high temperatures:



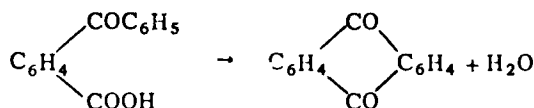
The compound results also on reacting a mixture of naphthalene and ethylene at an elevated temperature and on dehydrobromination of 1-bromoethylnaphthalene with alcoholic alkali. The compound has also been prepared in 53% yield by the action of phenyllithium on 1,8-dibromodimethylnaphthalene.²⁵¹

1,2-Acenaphthoquinone is obtained from naphthalene and oxalyl chloride by Friedel-Crafts reaction; acenaphthene results on reducing the semicarbazone of the quinone.⁸⁵

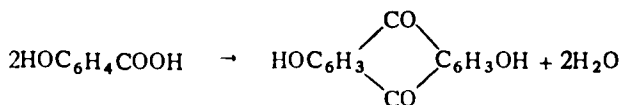
Anthracene results when a mixture of vapors of benzene and ethylene is passed through a tube heated to 800-1000°.⁸⁵

Anthracene and its derivatives may be prepared conveniently by Friedel-Crafts reaction. Thus, anthracene results through the reaction of benzene and acetylene tetrabromide or chloroform;⁸⁶ the compound may also be obtained through the self-condensation of benzyl chloride.⁸⁷ Anthracene is formed on heating *o*-brombenzyl bromide with sodium.⁸⁸

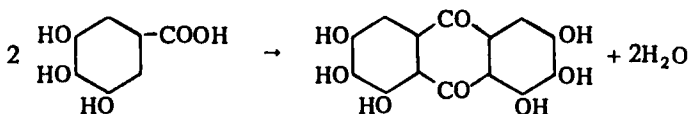
Anthraquinone results through the reaction of benzene with phthaloyl chloride and zinc dust. Hydroxy derivatives of the compound are formed on heating phthalic anhydride with a mono- or polyhydric phenol and sulfuric acid at 150°, although phthaleins are formed when an excess of phenol is used. Anthraquinone is formed in nearly quantitative yield on heating *o*-benzoylbenzoic acid with phosphorus pentoxide or concentrated sulfuric acid:⁸⁹



Substituted benzoylbenzoic acids give substituted anthraquinones. Di- and tetrahydroxyanthraquinones are formed when *m*-hydroxy- and *m,m'*-dihydroxybenzoic acids are heated with sulfuric acid:⁹⁰



Gallic acid gives rufigallic acid:⁹¹

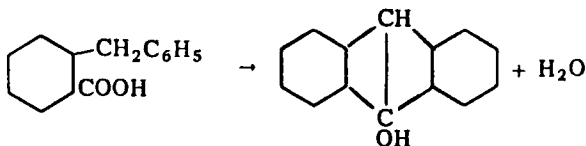


Reaction occasionally proceeds on straight distillation, but catalysts must be employed in most cases. Catalysts used other than those already mentioned are aluminum chloride and thallium chloride. Reaction proceeds readily in the temperature range 90 to 140°, but in some cases it is necessary to heat the compound to 200°. Reaction is usually complete within one to two hours. Reaction proceeds with great vigor in the presence of oleum and is complete within a few minutes. The use of sulfuric acid is undesirable if the aromatic groups are readily sulfonated. In some instances ring closure is prevented by steric hindrance; in many such cases cyclization may be brought about after the compound has been reduced, although tetrahydrobenzoic acid may be cyclized only after it has been dehydrogenated.²³³

The diaryl ketones are obtained through the reaction of phthalic anhydride and substituted phthalic acid anhydrides with aromatic compounds in the presence of aluminum chloride or other catalysts. 4-Halo-, 3- and 4-nitro-, and 3,5-dinitrophthalic anhydrides give only one of the possible isomers.²³⁴ While 3- and 4-methylphthalic anhydrides give both of the possible isomeric methylbenzoylbenzoic acids.²³⁵ Occasionally serious resinification occurs when aluminum chloride is used as a condensing agent. This can be avoided almost completely by the addition of small amounts of water.²³⁶

Condensation of two molecules of *m*-hydroxybenzoic acid under the action of sulfuric acid results in the formation of 1,5-dihydroxyanthraquinone, together with the isomeric 1,7-dihydroxyanthraquinone, as well as anthrarufin and anthraflavic acids. Two unlike hydroxybenzoic acids or a hydroxybenzoic acid and benzoic acid may also be condensed in a similar manner.²³⁷

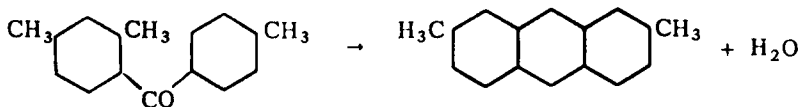
o-Benzylbenzoic acid and its derivatives are converted to anthrols on treatment with concentrated sulfuric acid:²³⁸



Triphenylmethane-*o*-carboxylic acid and its derivatives are converted to meso-phenylanthranols.²³⁹

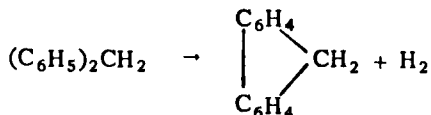
One of the important methods of preparation of hydroxyanthraquinones depends on the decomposition of phthaleins with hot sulfuric acid.⁹²

Methylated anthracenes have been obtained from the appropriate methylated benzophenones under the action of heat:



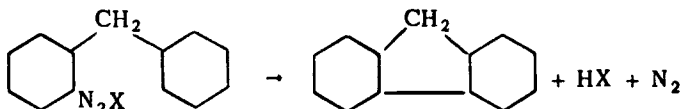
The desired benzophenone may be obtained by the Grignard reaction from halogenated benzenes and methylated benzonitriles.²⁰⁶

Fluorene results when vapors of diphenylmethane are passed through a red hot tube:⁹³



it may also be obtained through the reduction of fluorenone, a compound that may be prepared by heating diphenyl-*o*-carboxylic acid or its salts.

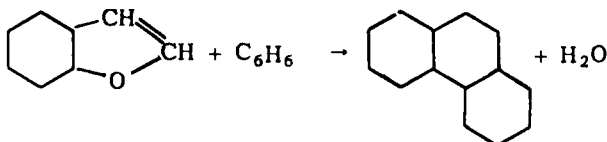
Pschorr's reaction has been employed for the synthesis of fluorene and its derivatives:⁹⁴



Fluorenone may be obtained through the cyclization of 2-biphenylcarboxylic acid obtained from benzene and diazotized methyl anthranilate and hydrolysis of the 2-biphenylcarboxylic ester formed. Substituted fluorenonees may also be formed by this method.²⁰⁷

2-Methyldiphenyl, dehydrogenated over palladium at 450° , gives fluorene.²⁰⁷

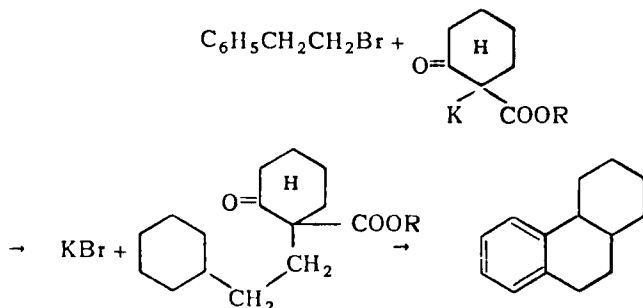
Phenanthrene is formed, together with other hydrocarbons, on passing vapors of *sym*-diphenylethane through a red hot tube; it is also formed on heating coumarone with benzene:⁹²



The compound is obtained, together with anthracene, by the Wurtz-Fittig synthesis from *o*-brombenzyl bromide and sodium, via the dihydro compound.

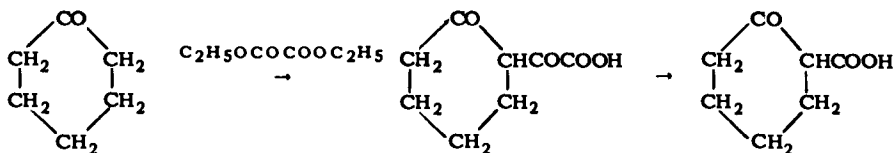
Naphthylbutyric acids, heated with 85% sulfuric acid or with stannic chloride, give ketotetrahydrophenanthrenes, which on reduction followed by dehydrogenation with selenium, are converted to phenanthrene.⁹⁵

The condensation product of phenethyl bromide with potassium cyclohexanone-carboxylic ester may be converted to octahydrophenanthrene by hydrolysis, decarboxylation, reduction of the resulting keto compound to alcohol, and cyclization with phosphorus pentoxide:⁹⁶

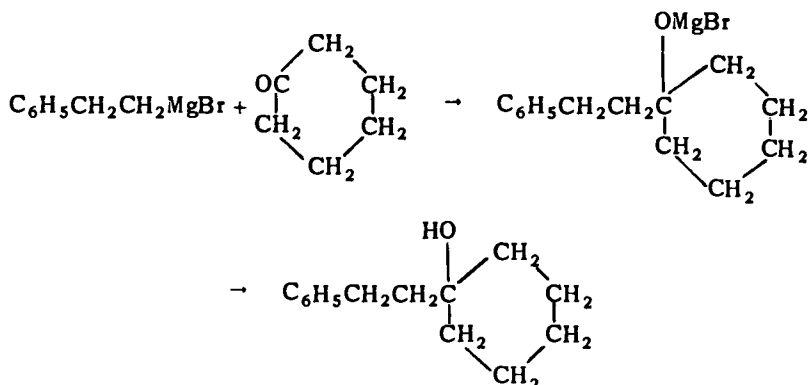


The octahydro compound may be converted to phenanthrene by dehydrogenation with selenium.

Cyclohexanone carboxylic acids may be prepared from cyclohexanone and its alkylated derivatives by condensation with oxalic ester and oxidation of the resulting keto acid:

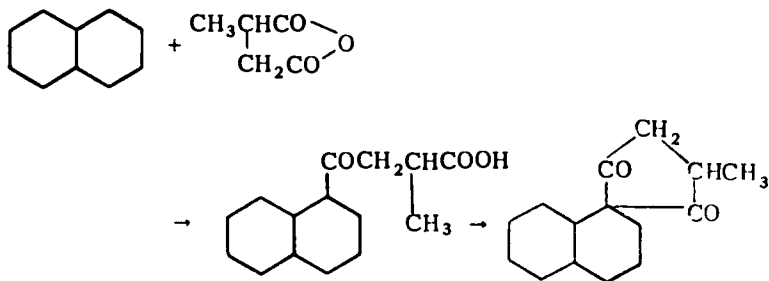


In the *Bogert-Cook* synthesis the reaction of a β -aryl ethyl magnesium bromide with cyclohexanone is utilized for the preparation of intermediates for the production of phenanthrene derivatives:²⁰⁸



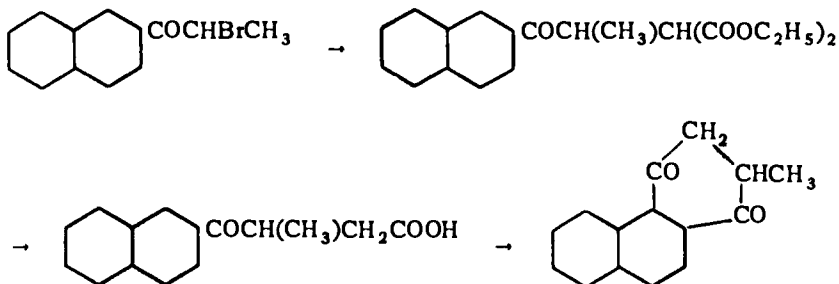
The resulting hydroxy compound, treated with concentrated sulfuric acid, undergoes cyclodehydration to form octahydrophenanthrene. This method is of more general applicability than the preceding, and offers a simpler means for the preparation of the required intermediates.

The keto acids resulting from the reaction of succinic and substituted succinic anhydrides with naphthalene derivatives may serve for the synthesis of phenanthrene derivatives by internal condensation:



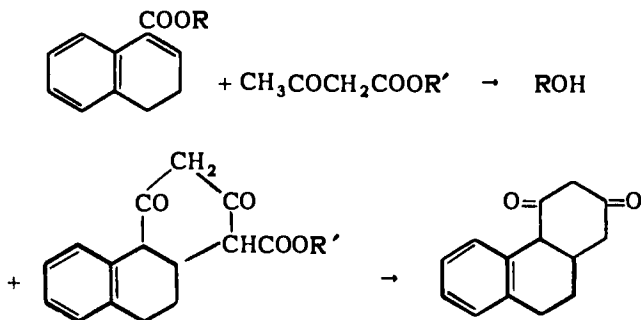
β -Methylnaphthalene gives the 6-acylated product in 79% yield with the anhydride at a low temperature, while acyl halides give the 1-acylated product.

The condensation of aromatic α -bromoketones with malonic ester in the presence of sodium also affords intermediates that may be cyclized to phenanthrene derivatives.



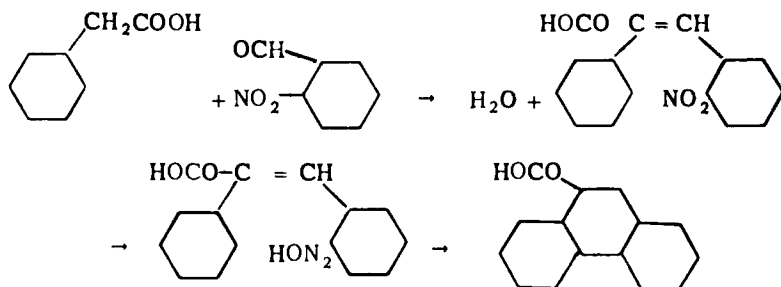
Phenanthrene has been obtained from 2,2'-dimethyldiphenyl by dehydrogenation with sulfur.²⁰⁹

The condensation of 3,4-dihydro-1-naphthoic ester with acetoacetic ester in the presence of sodium ethoxide results in the formation of diketooctahydrophenanthrenecarboxylic ester which, on hydrolysis and decarboxylation, gives octahydrodiketophenanthrene:⁹⁷

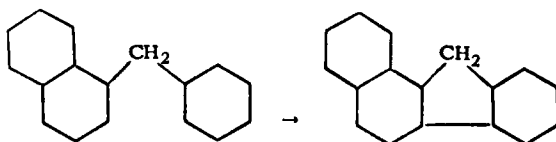


The diketone is converted to phenanthrene on distillation with zinc dust.

Pschorr's synthesis has been applied to the preparation of many phenanthrene derivatives.⁹⁸ Thus, the condensation product of phenylacetic acid and *o*-nitrobenzaldehyde, reduced to the amino compound and diazotized, gives phenanthrene-9-carboxylic acid:

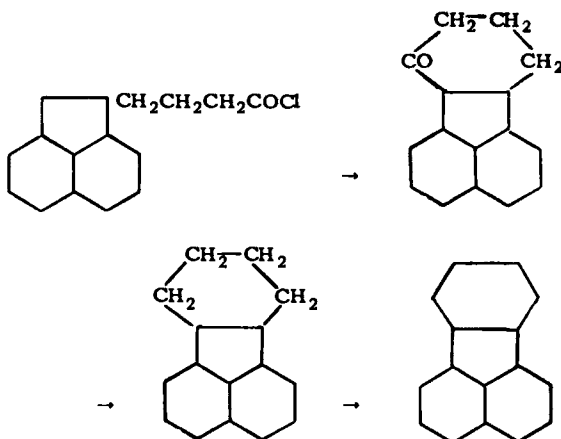


1,2-Benzofluorene results on passing vapors of benzylnaphthalene through a red hot tube:⁹⁹

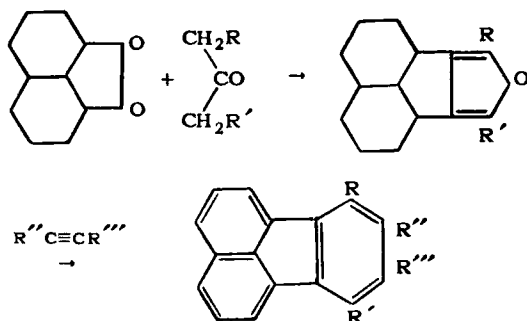


The compound is also obtained through the reduction of 1,2-benzofluorenone.¹⁰⁰

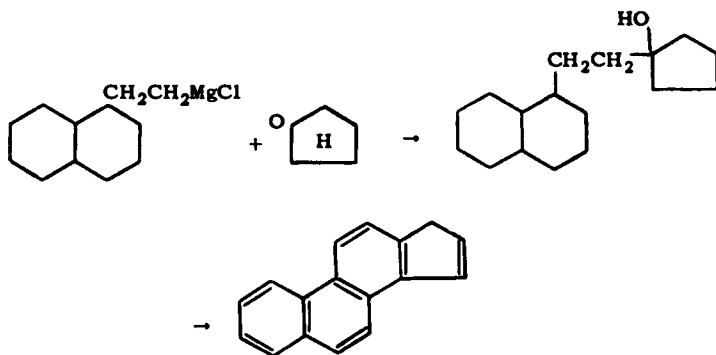
Fluoranthrene or *idryl* has been synthesized from β -9-fluorenylpropionyl chloride, which was converted to 4-keto-1,2,3,4-tetrahydrofluoranthrene by the Friedel-Crafts reaction, the ketone was reduced by Clemmenson's method, and finally dehydrogenated to the hydrocarbon:



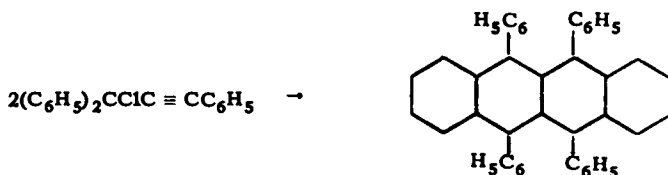
Several alkyl and aryl derivatives of fluorethene have been prepared by the Diels-Alder addition of acetylene to the diene resulting from the reaction of ketones with acenaphthoquinone, the intermediate endocarbonyl compounds losing carbon monoxide very readily:²⁵²



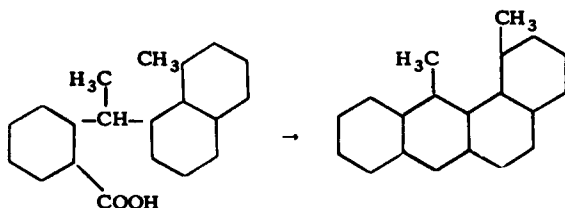
1,2-Cyclopentenophenanthrene has been prepared by the reaction of naphthylethylmagnesium chloride and cyclopentenone, ring closure and dehydrogenation being effected simultaneously by treatment with sulfuric acid:¹⁰¹



1-Chloro-1,1,3-triphenylprop-2-yne condenses to rubrene at a slightly elevated temperature:²⁵³

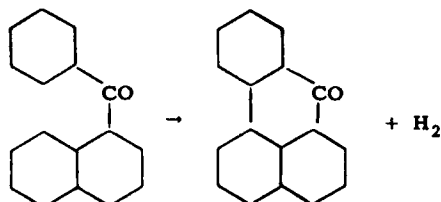


1,9-Dimethyl-1,2-benzanthracene has been made through the cyclization of the tetrahydro derivative of 1-(2-carboxyphenyl)-ethyl-1-methylnaphthalene-8 and reduction and dehydrogenation of the product.²⁵⁴



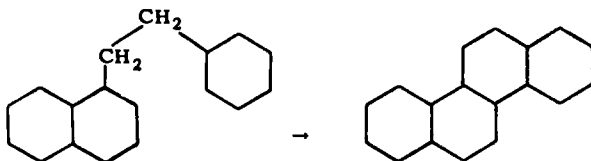
It has not been found possible to cyclize the unreduced carboxyphenylethylmethyl-naphthalene.

1-Benzanthrone has been obtained through the intramolecular dehydrogenation of 1-benzoylnaphthalene in the presence of aluminum chloride or ferric chloride:²⁴⁰



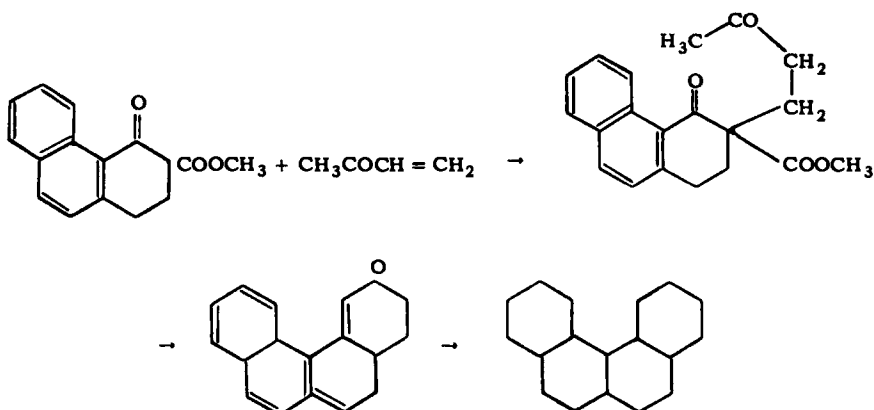
This method, originated by Scholl and involving a *peri* cyclization of an aromatic ketone, has been employed also for the preparation of many other polynuclear hydrocarbons.²⁴¹ Migration of the substituent has been observed with many substituted benzoylnaphthalenes.²⁴²

Chrysene¹⁰² has been obtained through the pyrolytic condensation of phenylnaphthyl-(1)-ethane:



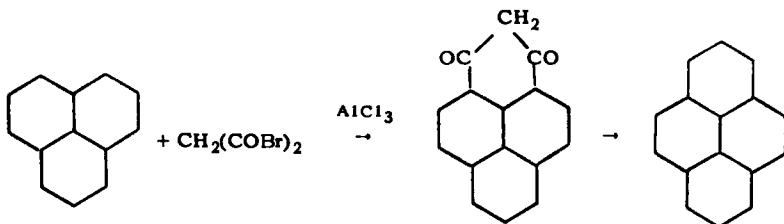
The compound also results on heating naphthalene with coumarone, and in good yield on heating with indene.¹⁰³ 1-Nitronaphthyl-2-o-cinnamic acid has been converted to chrysene-1-carboxylic acid, and this, on distillation gives chrysene.¹⁰⁴ Diphenylmuconic acid, $\text{HOCOCH}_2\text{C}(\text{C}_6\text{H}_5) = \text{C}(\text{C}_6\text{H}_5)\text{COOH}$, treated with acetic anhydride containing some sulfuric acid, gives diacetyl-2,8-dihydroxychrysene. The keto ester formed on condensation of β -(naphthyl-1-) ethyl bromide with cyclohexanone-o-carboxylic ester, cyclized with sulfuric acid and dehydrogenated with selenium gives chrysene.

3,4-Benzophenanthrene has been prepared from 4-keto-3-carbethoxy-1,2,3,4-tetrahydrophenanthrene by reaction with methyl vinyl ketone, cyclization, decarboxylation, reduction of the keto group of the resulting cyclic ketone and finally dehydrogenation:²⁵⁵



The 2-methyl and 2-ethyl derivatives of 3,4-benzophenanthrene have been prepared, in 81 and 38% yield respectively, from the keto compound by reaction with methyl- and ethylmagnesium iodide and subsequent dehydration.

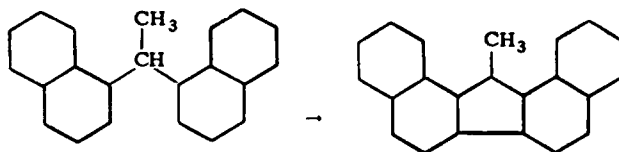
Pyrene has been obtained from peribenzonaphthalene by condensation with malonyl bromide and subsequent distillation with zinc dust:¹⁰⁵



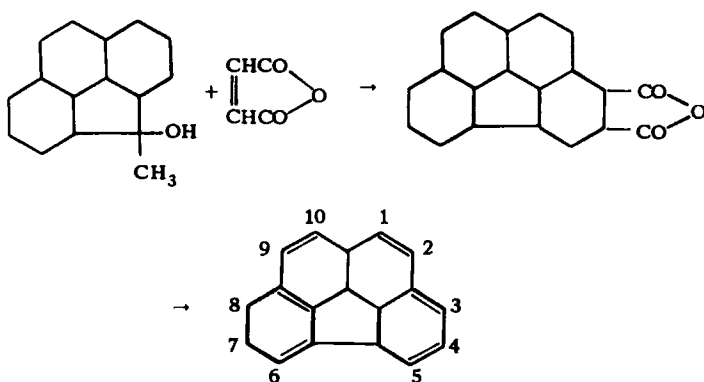
The compound has also been obtained from 1,4,5,8-naphthalenetetracarboxylic acid by

condensation of its anhydride with diethyl malonate, followed by distillation with zinc dust.¹⁰⁶

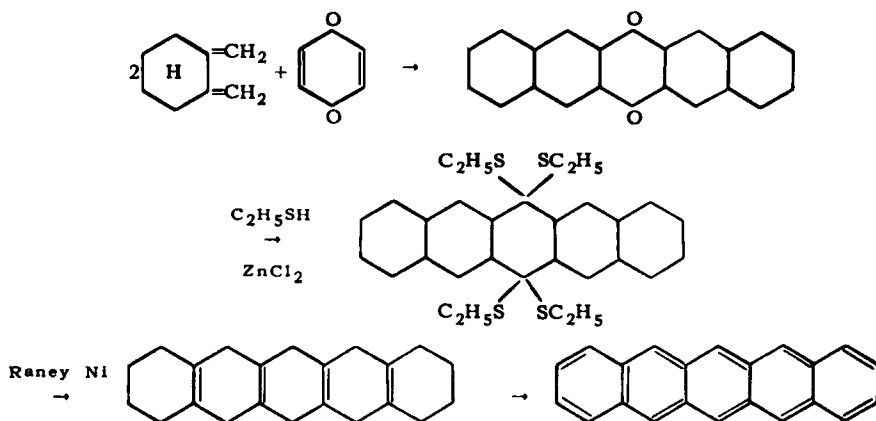
9-Alkyldibenzofluorenes have been prepared through the isomerization of 1,1-dinaphthylethylenes under the influence of reagents such as stannic or aluminum chloride:²⁵⁶



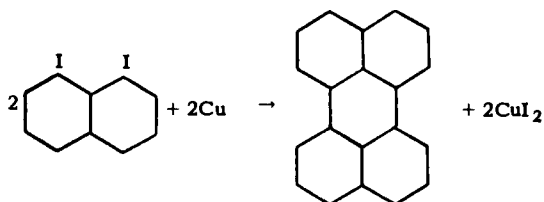
Benzo(mno)fluorene has been prepared by Diels-Alder synthesis from 4-hydrox-4-methylcyclopenta(def)phenanthrene and maleic anhydride and subsequent decarboxylation:²⁵⁷



Pentacene has been obtained in 30% overall yield through the condensation of benzoquinone with 1,2-dimethylenecyclohexene, conversion of the resulting diketo compound to the corresponding tetrathioetal, treatment with Raney nickel, and finally dehydrogenation by heating with a 5% palladium-carbon catalyst at 245° for three hours.²⁵⁸

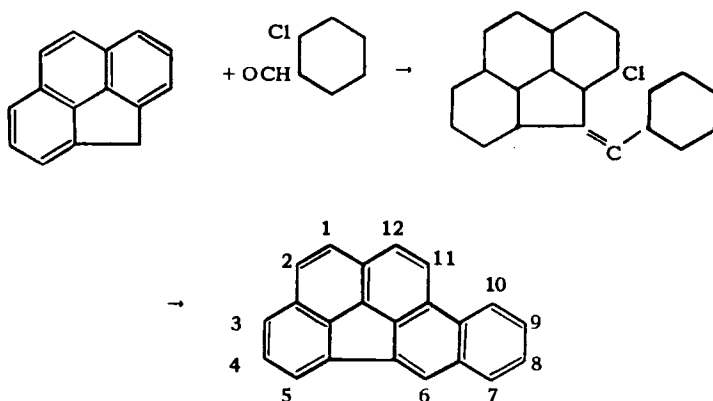


Perylene results when 1,8-diiodonaphthalene is heated with copper bronze:¹⁰⁷

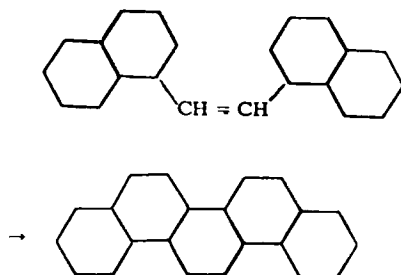


The compound has been obtained also from the chlorophosphoric ester of 2,2'-dihydroxy-1,1'-dinaphthyl by heating with condensing agents and reducing the resulting 1,12-dihydroxyperylene with zinc dust.¹⁰⁸ The compound is formed also when 2,2'-dihydroxy-1,1'-dinaphthyl is heated with metaphosphoric acid.¹⁰⁹

Dibenzofluoranthene has been synthesized by cyclizing the condensation product of 4-cyclopentano(def)phenanthrene and o-chlorobenzaldehyde with potassium hydroxide and quinoline.²⁵⁷

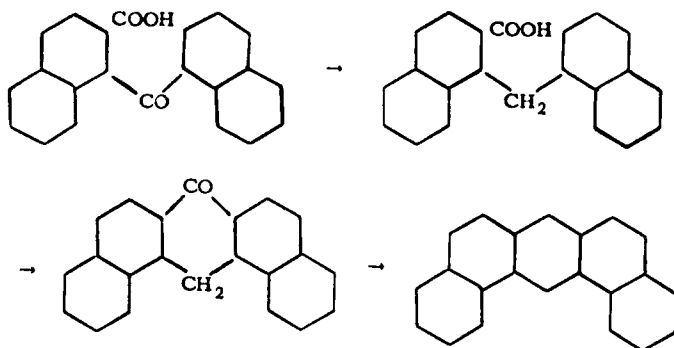


Picene has been prepared by strongly heating 1,1'-naphthostilbene:¹¹⁰

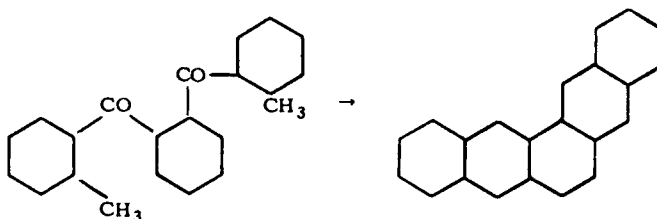


or by heating 1-methylnaphthalene with sulfur. The compound has also been prepared from naphthalene and ethylene dibromide by Friedel-Crafts reaction, and by the reaction of β -(naphthyl-1)-ethylmagnesium chloride with tetralone.

1,2,7,8-Dibenzanthracene has been prepared from 1,1'-dinaphthyl ketone 2-carboxylic acid by reduction of the carbonyl group to methylene, ring closure to anthracene and subsequent distillation with zinc dust;



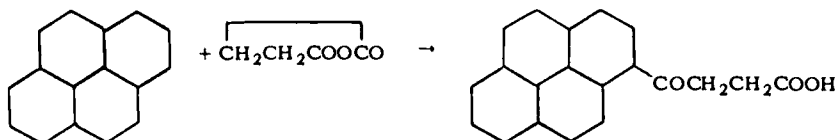
1,2,5,6-Dibenzanthracene has been obtained by heating 2-methyl-1,2'-dinaphthyl ketone. 1,2,3,4-Dibenzanthracene has been obtained as the main product from the Friedel-Crafts condensation of *o*-toluyl chloride and phenanthrene upon heating the mixture of ketones first formed in the reaction.¹¹¹ 2,3,6,7-Dibenzanthracene results when di-*o*-toluylbenzene is heated strongly:¹¹²

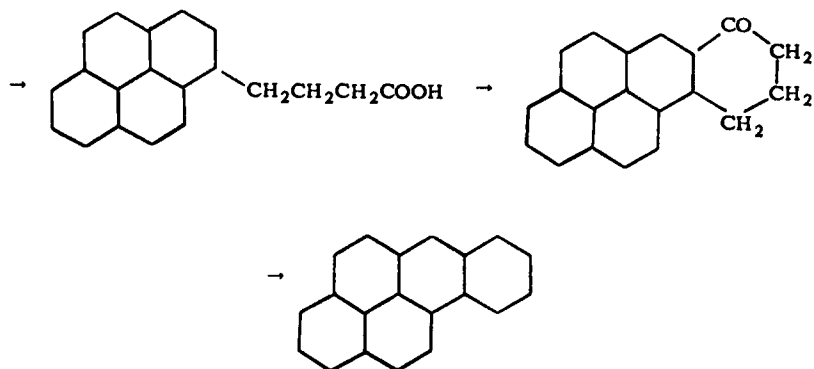


Di-*o*-Toluylbenzene itself is obtained through the reaction of *o*-tolylmagnesium bromide with phthalic anhydride.

The pentanuclear hydrocarbons naphtho-2,3':1,2-anthracene, naphtho-2',3' : 1,2-phenanthrene and 1,2,3,4-dibenzanthracene and the hexanuclear anthraceno-1',2' : 1,2-anthracene have been prepared by this method from 1,2-d-*o*-toluylbenzene, *o*-tolyl-2-octahydrophenanthryl ketone, 3-tolyl-9-phenanthryl ketone and 1,5-dibenzoyl-2,6-dimethylnaphthalene, respectively.²⁴³

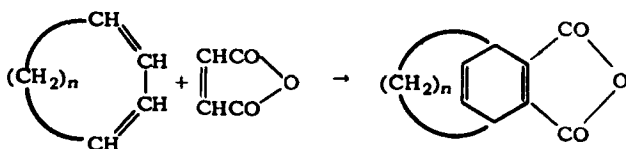
1,2-Benzpyrene has been synthesized from pyrene and succinic anhydride, the condensation of which in the presence of aluminum chloride gives β -(1-pyrenoyl)-propionic acid; the sodium salt of this reduced with zinc dust and ammonia gives the hydroxy acid, which, on removal of water and hydrogenation is converted to γ -(1-pyrenyl)-butyric acid. On heating this to 120° with stannic chloride, it is converted to 4'-keto-1',2',3',4'-tetrahydro-1,2-benzpyrene, which on dehydrogenation with selenium gives 1,2-benzpyrene:¹¹³



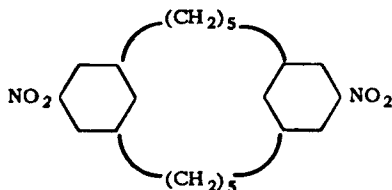


4,5-Benzpyrene has been obtained from the condensation product of *aym*-hexahydro-pyrene and succinic anhydride, namely, β -1,2,3,6,7,8-hexahydro-4-pyrenoylpropionic acid. This, on reduction by the Wolff-Kishner method, ring closure under the action of sulfuric acid, reduction with sodium and alcohol and finally dehydrogenation with selenium gives the hydrocarbon.

Para-bridged benzene rings have been prepared by the Diels-Alder reaction of maleic anhydride with large ring dienes.²⁵⁹



The condensation of nitromalonic aldehyde with cyclooctanone and larger cyclic ketones gives six-membered rings with a meta bridge. Condensation with cyclohexadecane-1,9-dione gave the compound



incorporating two benzene rings as part of a large ring structure.²⁶⁰ The name *paracyclophane* has been suggested for this class of compounds.

Aromatic Deuterium Compounds

Hexadeuterobenzene has been prepared through the polymerization of di-deuteroacetylene.²¹⁰ It has also been made from benzene by reaction with deuterium oxide in the presence of nickel,²¹¹ and from benzene and deuterium chloride in the presence of aluminum chloride.²¹² Another method of formation is the decomposition of calcium mellitate with calcium deuterioxide.²¹³

Characteristics of Aromatic Compounds

Aromatic hydrocarbons present many differences from aliphatic hydrocarbons. The aromatic nucleus shows exceptional stability, the ring being cleaved only under exceptional circumstances, although compounds the formula of which cannot be represented in terms of Kekulé structures are unstable. Many aromatic compounds may be fused with alkalis without affecting the aromatic ring. The hydrogen atoms attached to the aromatic nucleus are readily replaced by halogens, and nitro and sulfonic groups. On the other hand, halogens attached to an aromatic nucleus are, in general, far less mobile than those attached to an aliphatic group, the same holding true of other negative residues attached to the nucleus.

The hydroxy and amino derivatives of naphthalene hydrocarbons are readily interconvertible. Thus, aminonaphthalenes may be converted to the corresponding hydroxynaphthalenes by heating with aqueous sodium bisulfite, and, conversely, hydroxynaphthalenes may be converted into aminonaphthalenes by warming with ammonium sulfite solution.¹¹⁴

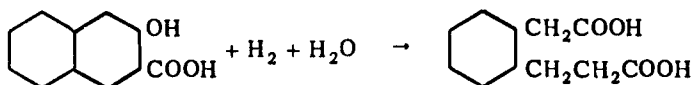
Phenols, in contrast to the corresponding aliphatic bodies, the alcohols, are distinctly acidic in nature and react with alkalis to form salts. Phenols are much more difficult to esterify than alcohols, although α -naphthol may be esterified with alcohol and hydrochloric acid at 150°.

Aromatic amines, i.e. compounds in which the amino group is attached to the aromatic nucleus, are far less basic than aliphatic amines, and do not combine with carbon dioxide. Aromatic amines are also distinguished from aliphatic amines in that they are capable of forming diazo compounds with nitrous acid.

Aromatic compounds in general undergo the Friedel-Crafts reaction, while aliphatic compounds fail to take part in this reaction.

Aromatic compounds do not show an unsaturated character despite the presence of double bonds in the ring; they are resistant to oxidizing agents and do not readily give addition compounds with halogens, although hexahalo compounds of the type of $C_6H_6X_6$ have been obtained by the prolonged action of chlorine or bromine on benzene.¹¹⁵ Naphthalene derivatives undergo certain addition reactions with some ease, addition taking place at the α -positions. Benzene is attacked very slowly by aqueous permanganate or chromic acid, reaction resulting in the formation of acids. Reaction with manganese dioxide and sulfuric acid produces carbonyl compounds. Aromatic compounds are not readily reduced, the use of an active nickel catalyst at 180 to 200° being required, for example, for the hydrogenation of benzene. The optimum experimental conditions depend largely on the nature of the compound. Long side chains are often split off at temperatures in excess of 200°. The rate of hydrogenation and of the reverse process of dehydrogenation, which takes place at higher temperatures, are governed by the nature of the catalyst employed.¹¹⁶ Homologs of benzene are generally reduced more readily than benzene itself. Benzene is hydrogenated on heating at 260-280° with hydriodic acid. Ener-

getic reduction of 2,3-hydroxynaphthoic acid with sodium and amyl alcohol has resulted in the formation of *o*-phenyleneacetic propionic acid:¹¹⁷



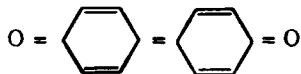
Open chain groups attached to the aromatic nucleus preserve their aliphatic character. The two groups exert a mutual influence, however. Thus, alkyl groups attached to the benzene nucleus exert a directing influence causing attachment of substituents at certain preferred positions, and also facilitate the nitration of the aromatic nucleus. In turn, the aromatic nucleus exerts an activating influence on methyl or methylene groups directly attached to it. Decided differences have been observed in the properties of aromatic compounds with olefinic side chains, depending on the position of the double bond. Compounds in which the double bond is in the 1:2 position possess a higher density, a higher boiling point, abnormally high molecular refraction and a lower heat of combustion, as compared with those in which the double bond is in the 2:3 or 3:4 position. Compounds with the double bond in the 1:2 position are also readily reduced with sodium and alcohol.¹¹⁸

Oxidizing agents attack the side chains of homologs of benzene, the aromatic ring remaining intact; the alkyl groups are oxidized to carboxyl groups. A solution of chromium trioxide in moderately concentrated sulfuric acid may be used as the oxidizing agent. Side chains in *meta* or *para* position with respect to each other are oxidized to carboxyl groups by chromic acid, while those in *ortho* position are not attacked, vigorous oxidation causing disruption of the molecule. Side chains situated in *para* position are oxidized more readily than those in *meta* position. A negative group in *ortho* position prevents the oxidation of the alkyl group with chromic acid.¹¹⁹ In derivatives with two different alkyl groups, the higher alkyl is usually attacked first by nitric or chromic acid, although the methyl group is first attacked in cymene with the formation of *p*-isopropylbenzoic acid. Potassium ferricyanide oxidizes the methyl group to carboxyl, if a nitro group is present in the *ortho* position, but the alkyl group remains intact if a nitro group is present in the *meta* position.¹²⁰

No experimental evidence exists of the presence of *stereoisomerism* among strictly aromatic compounds. Where isomerism is observed, it is traceable to conditions in a side chain. One notable exception should be pointed out, described as *atropic isomerism* and observed in 2,6,2',6'-substituted diphenyl derivatives.²⁵⁰ *o,o'*-Dinitro diphenic acid has been resolved into optical antipodes. Such mirror-image isomerides have been isolated from many other *ortho* substituted diphenyl derivatives. To explain this molecular asymmetry it has been assumed that the free rotation of the phenyl nuclei about their axes is restrained by certain *ortho* substituents, the two rings lying in different planes at right angles. Of the *cis* and *trans* forms of the atropic isomers of *o*- deriva-

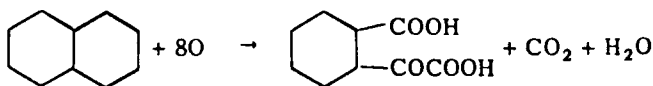
tives of terphenyl, the former are resolvable into optical antipodes while the latter are not, since they possess a center of symmetry.

The molecule of *diphenyl* possesses an unbroken conjugated system, and is capable of yielding bimolecular quinoid compounds



Halogen atoms and other substituents such as NO_2 , and SO_3H , are less strongly bound to the nucleus in naphthalene and its derivatives than in benzene derivatives.¹²¹

Naphthalene and other *polycyclic* aromatic hydrocarbons are comparatively easily oxidized. These compounds are converted to quinones on treatment with a mixture of chromic and glacial acetic acids. Under the proper conditions, the oxidation of naphthalene leads to the formation of phthalonic or phenylglyoxyl-o-carboxylic acid:¹²²

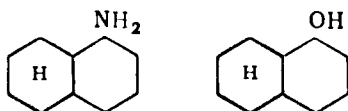


α -Naphthol also gives phthalonic acid,¹²¹ while β -naphthol yields cinnamic o-carboxylic acid on oxidation with potassium permanganate at ordinary temperature:¹²³



ac-Tetrahydro- β -naphthol is oxidized to hydrocinnamic-o-carboxylic acid;¹²⁴ on the other hand, aromatic tetrahydronaphthalene derivatives give on oxidation adipic and oxalic acid; dihydronaphthalene gives o-phenylenediacetic acid,¹²⁵ while 1,3-dihydroxynaphthalene is converted to toluic and acetic acids.¹²⁶

Substitution reactions generally proceed under milder conditions in the case of *naphthalene* than with benzene. Naphthalene is reduced by sodium amalgam to 1,4-dihydronaphthalene. Reduction with metallic sodium and amyl alcohol gives 1,2,3,4-tetrahydronaphthalene. Catalytic reduction results in the formation of 1,2,3,4-tetrahydronaphthalene or decahydronaphthalene.¹²⁷ α -Naphthylamine and α -naphthol give on reduction *ar*-tetrahydro- α -naphthylamine and *ar*-tetrahydro- α -naphthol,

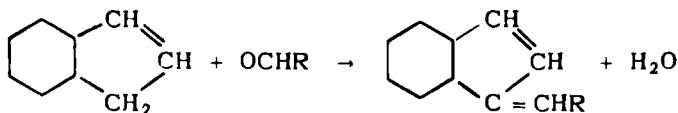


while the β -compounds form both the *ar*- and *ac*-derivatives, the latter pre-

dominating in the mixture. Further hydrogenation is possible only by use of more energetic agents. *1,5-Naphthylenediamine* gives *ac*- and *ar*-tetrahydronaphthylenediamine. Oxidation of *ac*-tetrahydronaphthylamine with potassium permanganate causes cleavage of the hydrogenated ring, giving *o*-cinnamocarboxylic acid. Dehydrogenation of 1-phenyldihydronaphthalene- $\Delta^{1,2}$ over silica gel at 350° gives 2-phenylnaphthalene.¹²⁸ This migration is noted with other 1-substituted naphthalene derivatives.

Dihydronaphthalene behaves as a derivative of benzene with an aliphatic unsaturated side-chain; with bromine it gives a dibromide which may be converted to a glycol by treatment with aqueous potassium carbonate.

The methylene group in *indene*, like that in cyclopentadiene, is reactive, and the compound condenses with aldehydes in the presence of alkalis to form intensely colored hydrocarbons derived from benzofulvene

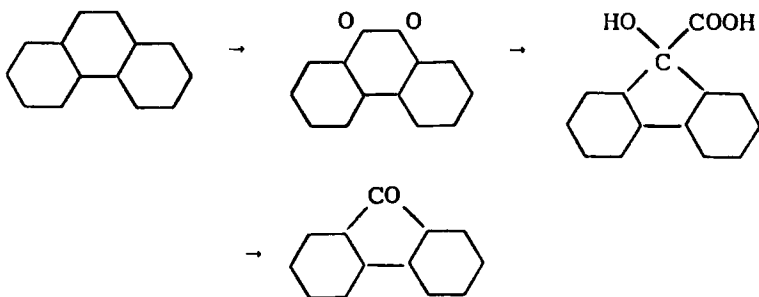


Indene gives a sodium derivative on heating with sodium or sodamide. The hydrocarbon is autoxidizable and readily polymerizes even at room temperature and in the dark. Polymerization is accelerated by sulfuric acid, diatomaceous earth, metallic halides, etc. The polymers are of varying molecular weight, amorphous and contain one olefinic bond per molecule of indene.¹²⁹ In common with unsaturated terpenes, indene combines with nitrosyl chloride and nitrogen tetroxide to form indene nitrosochloride and indene nitrosite.

Acenaphthene, like indene, shows a tendency toward polymerization. Exposed to the direct rays of the sun, it changes in the course of a few days into two colorless dimers, which are apparently *cis* and *trans* isomeric dinaphthalene-cyclobutanes, convertible on reduction to 1,1'-biacenaphthyl.

There are many manifestations of reactivity of a high order at the *meso* or 9, 10-positions in *anthracene*. Oxidation to anthraquinone can be accomplished by use of a mixture of chromic anhydride and acetic acid, or of sodium bichromate and sulfuric acid. Bromine adds at these positions forming a dibromide. The carbon atoms in the 9, 10-positions are readily hydrogenated even by use of sodium amalgam and ethyl alcohol. Anthracene can function as a diene component in the Diels-Alder reaction,¹³⁰ union taking place at 9 and 10 positions, although the reaction is reversible and anthracene can be recovered from the maleic anhydride adduct by distilling off the more volatile maleic anhydride under vacuum. The *nitration* of anthracene proceeds in an abnormal manner, the initial product appearing to be dihydroanthranol.¹³¹ Anthracene and its derivatives undergo photo-oxidation, giving transnuclear peroxides.¹³² *Meso* substituents favor the formation of photooxides.¹³³

The 9 and 10 positions in *phenanthrene* also manifest special reactivity; alkali metals add exclusively at these positions, and oxidation with osmium tetroxide and other oxidizing agents gives 9,10-phenanthraquinone.¹³⁴ If a C-substituent is present at 9 or 10 position, this is eliminated in the course of the oxidation and a 9,10-quinone is again formed. Benzilic rearrangement takes place, however, when the compound is treated with alkaline potassium permanganate, and the final product is fluorenone;¹³⁵



This transformation takes place also when 9,10-phenanthraquinone is distilled over lime, or its vapors are passed over heated lead oxide. The 9:10 double bond in phenanthrene is also reactive and adds bromine, and methyl hypobromite; it can be readily hydrogenated over copper-chromic oxide catalyst.

Oximes of 1-, 2-, 3- and 9-acetylphenanthrenes give acetamino compounds by the Beckmann rearrangement, while oximes of benzoylphenanthrones give, in addition, anilides of the corresponding acids. In the latter case, anilides form the main product of the transformation of oximes of the 1- and 9-isomers.

Oxidation of *pyrene* with chromic acid gives a mixture of 3,8- and 3,10-quinones.¹³⁶

The reduction of pyrene²¹⁴ in the presence of copper chromite at 110 to 120° under an initial pressure of 125 atm leads to the formation of the two isomeric hexahydropyrenes. With Raney nickel in cyclohexane at 150 to 160° under an initial pressure of 145 atm, pure hexadecahydropyran results.

Substitution Reactions

Substitutions in the Benzene Ring;

The Crum Brown and Gibson Rule.

Aromatic compounds do not readily undergo addition reactions, but they are capable of interchanging nuclear hydrogen atoms for halogens and for the nitro or sulfonic groups, by reaction with halogens, and with nitric or sulfuric acids. The readiness with which substitution takes place depends on the character of the compound and is influenced by groups already present in the molecule of the aromatic compound. The substituents have a decisive effect on the point of attack, some inducing substitution at *ortho* and *para* positions, others at the *meta* position, regardless of the nature of the entering group.

The point of attachment of an entering group is dependent also, in some measure, on the character of the entering group and on the reaction conditions, especially the temperature. In nitration reactions the directing effect is influenced by the nature of the solvent. For example, when phenylacetic acid is nitrated in acetic anhydride, which diminishes ionization, an increase in the proportion of the *m*-nitro derivative is observed. Differences in orientation are also observed when various metal nitrites are employed in conjunction with acetic anhydride or acetic acid as nitrating agents.

Attempts have been made to formulate general rules which would make it possible to predict whether the orienting influence of a substituent is of the *ortho-para* or *meta* directing type. The orienting influence of an element or group with a positive charge directly attached to the nucleus is exclusively *meta* directing;²⁴⁴ that of an element or group with a negative charge, *ortho-para* directing. The *meta* orienting influence decreases regularly with increase in the atomic number of the charged atom.²⁴⁵ With dipoles, the orienting effect, in so far as it arises from ionic charges present, may be expected to be that of a free pole corresponding with the end of the dipole nearer the nucleus, somewhat diminished by the compensating influence of the more distant opposite pole.

Sutton's rule²⁰² relates the directive influence of a group X with the difference in the dipole moments of ArX and AlkX. The positive sign is allotted to the moment of a dipole which has the positive end more distant from the aryl or alkyl group. The rule states that the group X is *ortho-para* directing when the difference in the dipole moments of ArX and AlkX is positive, and *meta* directing when the difference is negative.

The Crum Brown-Gibson rule,¹³⁶ which is not based on considerations of the distribution of electrons in the substituent groups, states that a group X is *meta* directing if its hydride is not easily oxidizable by a one-stage process to HOX, and *ortho-para* directing in the contrary case. The rule may be stated in a different though less definite form as follows: If a group X is more stable in its compounds with hydrogen than with hydroxyl, then it exerts an *ortho-para* directing influence, whereas if the reverse is true the group has a *meta* directing effect.¹³⁷

Hammick and Ilingworth related the directing influence of a substituent consisting of a combination of two elements X and Y to the relative position of the elements in the periodic table, stating that if Y is in a higher group in the table than X, then XY in C₆H₅XY is *meta* directing. If X and Y are in the same group and Y is of lower atomic weight than X, XY is still *meta* directing. All other substituents, including single atoms are *ortho-para* directing.¹³⁸ A positive charge in XY is presumed to cause *meta* substitution, while a negative charge is assumed to have *ortho-para* directing influence.

These rules fail to hold in certain instances, and Holleman, assuming that all substitution reactions are preceded by an addition reaction, attempted to relate the observed effects with the activating influence of the original substituent on the double bond in the aromatic ring. Groups activating the 1,2- and 3,4-double bonds favor 1,2- or 1,4-addition and are consequently *ortho-para*

directing, whereas groups which inhibit addition at these points are *meta* directing. The concept of "surplus energy"¹³⁹ at the *ortho-para* position or at the *meta* position, depending on the firmness or looseness of the bond between the substituent and the carbon atom to which it is attached, may be considered another aspect of the ideas expressed by Holleman.

A summary of the situation in modern concepts may be stated as follows: If in the orienting group the atom attached to the ring contains unshared electrons, the electromeric or resonance effect will overcome any inductive effect and there will be *ortho-para* substitution. If an atom with unshared electrons is linked by a double bond to the atom attached to the ring, there will also be a powerful electromeric effect and a substitution will take place in the *meta* position. In all other cases the inductive effect will control the result, with electron-attracting groups causing *meta* substitution, and electron-repelling groups inducing *ortho-para* substitution.

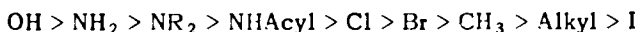
The more common *ortho-para* directing groups are OH, OR, NH₂, NR₂, SR; among the groups which induce *meta* substitutions are NO₂, COOH, CN, CHO, COR, SO₃H, SO₂R. Reducing groups such as $-\text{C}=\text{C}-$, $-\text{C}\equiv\text{C}-$ and the aromatic ring are *ortho-para* directing. In the compound $\text{C}_6\text{H}_5\text{CH}=\text{CHNO}_2$, the tautomeric deactivating effect of the nitro group is reduced to a second order magnitude, far weaker than that of the nearer activating double bond.

The proportion of the *para* and *ortho* isomers formed, when an *ortho-para* directing substituent is present, varies according to the character of the substituent already present in the molecule, as well as the conditions under which the reaction is carried out. The solvent employed also has a decided effect.

In the benzophenone series, a substituted benzoyl group, $-\text{COC}_6\text{H}_4\text{R}$, always has a deactivating *meta* directing influence, whatever the nature of the group R. Similarly, in the diphenyl ether series, a substituted phenoxy group, $-\text{OC}_6\text{H}_4\text{R}$, always has an activating *ortho-para* directing influence.

The presence of an *ortho-para* directing group in an aromatic compound causes an increase in the rate of substitution reaction, while *meta* directing groups cause a decrease in the rate.¹⁴⁰

The directive effect of substituent groups is not of equal magnitude; the hydroxyl group exerts the strongest influence. The directive effect of certain other *ortho-para* directing substituents ranges, in decreasing order of magnitude, as follows:



Among the *meta* directing groups the effect of the carboxyl group exceeds in magnitude that of the sulfonic group, and the effect of the latter is greater than that of the nitro group. When two directing groups are present in the molecule, the group with the stronger directive effect determines the point of entrance of new substituents. Thus, when *p*-toluidine is brominated, bromine enters the ring in the position *ortho* to the stronger directing amino group.

When two substituents are present in the aromatic molecule their directive influence is superimposed. In 1,2- and 1,4-derivatives, if one substituent is *ortho* directing and one *meta* directing, the *ortho-para* directing influence is re-

inforced. If, on the other hand, both substituents are *ortho-para* directing their influences act in opposite directions, and the effect of the stronger predominates. When *m*-nitrotoluene is further nitrated, the nitro group enters the positions *ortho* and *para* to the CH₃ group and not the *meta* position with respect to the original nitro group.

The directive influence of various substituents present in the benzene ring toward halogens, the nitro and the sulfonic groups is given in Table I,¹⁴¹ while in Table II¹⁴² are given the proportions of various isomers formed on mononitration of monosubstituted benzene derivatives.

Table I. Directive Influence of Substituent Present in the Benzene Ring

Substituent Present at Position 1	Position Taken by Entering Substituent				
	Cl	Br	I	NO ₂	SO ₃ H
Fl				4,2	4
Cl	4,2,3	4,2,3	4	4,2	4
Br	4,2,3	4,2,3		4,2	4
I	4	4	4	4,2	4
NO ₂	3	3		3,2,4	3,2,4
SO ₃ H		3		3,2,4	3,4
CH ₃	4,2	4,2	4,2	2,4,3	4,2,3
CH ₂ Cl	4			4,2,3	
CH ₂ SO ₃ H	2,4				
CHCl ₂	4			3?	
CCl ₃	4			3?	
COOH	3,2,4	3	3	3,2,4	3,4
NH ₂ H ₂ SO ₄	4,2		4	4,3,2	2,4
NH.Ac	4	4	4	4	4,2,3?
NH.Benz.				4,2,3?	4,2,3
N(CH ₃) ₂		3,4		2,3,4	
OH	4,2	4,2	4,2	2,4	2,4,2?
OAlk		4	4	2,4	4,2,3?
CN				3	
CHO	2,3			3,2	
COCH ₃				3,2,4	

The following groups are *meta* directing: CH = NOH, NH₂(Alk)H, NH(Alk)₂H, NH₂(Acyl)H, SO₂Cl, SO₂F. The following are *ortho-para* directing: O, Acyl, N ≡ N, CH(Alk)₂, C(CH₃)₂, CH₂ONO₂, CH₂COOH, CH₂CH₂COOH, CH = CHCOOH, C ≡ CCOOH, C₆H₅. The *ortho-para* directing effect of the group -C = C- is not destroyed by terminal electron attracting groups such as COOH, SO₂Cl, NO₂.

The successive introduction of saturated carbon atoms between a *meta* directing group and the nucleus diminishes the *meta* orienting effect. The proportion of the *meta* nitro derivative obtained in the nitration of nitrobenzene, phenylnitromethane, and phenylnitroethane are 93%, 48%, and 13% respectively.²⁴⁶ The greater damping effect of the unsaturated grouping -CH = CH- as compared with that of the saturated group -CH₂CH₂- is shown by the fact that

Table II. Proportion of Disubstituted Isomers Obtained from Various Monosubstituted Benzene Derivatives

Substituent Present	Proportions of Various Isomeric Disubstituted Benzenes Formed (%)			Temp. of Reaction
	Ortho	Para	Meta	
COOH	18.5	1.3	80.2	0
COOCH ₃	21.0	5.8	73.2	0
COOC ₂ H ₅	28.3	3.3	68.4	0
COOC ₈ H ₁₇ (n)	39.8	—	60.2	0
COOC ₁₆ H ₃₃ (n)	48	—	52	0
CN	—	—	80.5	0
COC1	—	2.1	90.2	-10
CCl ₃	6.8	28.7	64.5	25
CH ₂ CN	17	69	14	-8
CH(CN) ₂	32.1	—	67.9	-10
C(COOC ₂ H ₅) ₃	43.4	—	56.6	-10
CH(OH)CN	56.4	—	43.6	-9
CH(COC ₂ H ₅)CN	62.8	—	37.2	-9
C≡CCOOH	27	65	7.7	-3
C≡CCOOC ₂ H ₅	36	57.9	6.1	-3
CHO	21.4	—	78.6	10
COCH ₃	45	—	55	0
CH ₃	58	38.1	3.9	0
CH ₂ Cl	40.9	54.9	4.2	25
CH ₂ Br	93	—	7	17
CHCl ₂	23.3	42.9	33.8	25
CH ₂ CH ₂ Cl	30	70	—	-13
CH ₂ NH ₂	8	43	49	0
CH ₂ NHCH ₃	?	?	69	-5
CH ₂ N(CH ₃) ₂	?	?	58	0
CH ₂ NO ₂	—	14	50	0
CH ₂ CH ₂ NH ₂	23	64	13	-5
CH ₂ CH ₂ NHCH ₃	—	61	15	-8
CH ₂ CH ₂ N(CH ₃) ₂	20	66	14	-8
CH ₂ CH ₂ N(CH ₃) ₂ picrate	13	66	21	0
NO ₂	4.8	1.7	93.2	0
NH ₃ .HSO ₄	2.1	51.3	46.6	-20
NH ₃ NO ₃	5	62	32	-20
NHCOH	18.1	79.7	2	20
NHCOCH ₃	19.4	78.5	2.1	20
NHCOC ₂ H ₅	21.1	77.7	1.2	20
NHCOC ₆ H ₅	41.1	57.4	1.5	-20
N(COCH ₃) ₂	40.4	58.0	1.6	-20
N:CHC ₆ H ₅	5.5	93.9	0.6	20
OH	57.6	40.0	3.3	10

while β -phenylnitroethane yields 30% of meta nitro derivative, ω -nitrostyrene gives but a trace of the meta product.²⁴⁷

The successive introduction of halogen atoms into the side chain causes a continued increase in meta substitution. Thus, the proportions of meta sub-

stituted product obtained from benzyl chloride, benzal chloride and benzo trichloride are 4, 35, and 64%. Carbonyl, carboxyl and cyano groups have the same effect as halogens. The introduction of alkyl groups has the opposite effect. The effect is the more marked, the closer the atom or group to the aromatic nucleus.

The directive influence of a hydroxyl group outweighs that of other substituents. The directive power of this group is reduced by alkylation or acylation. Halogens and alkyls have almost equal directing activity.

When *ortho-para* and *meta* directing substituents are simultaneously operative, the influence of the former usually predominates, or masks the effect of the latter.

The directing influence of primary, secondary, and tertiary amino groups is greatly diminished by the presence of large amounts of concentrated sulfuric acid. Considerable amounts of *meta* substituted derivatives are formed in the sulfonation or nitration of amines in concentrated sulfuric acid solution.

The neutralization of carboxyl or sulfonic groups with a strongly alkaline solvent of low dissociating power, such as pyridine, causes a marked change in the directive influence of these groups.

When substitution proceeds to the point where four groups enter the aromatic nucleus, they tend to distribute symmetrically in the molecule.

Substitutions in Polynuclear Hydrocarbons

Within a single ring of *diphenyl*, the normal laws of substitution in benzene are operative. Since the phenyl group behaves as a strong *ortho-para* directive group, substitution in the *ortho* and *para* positions can be readily effected. Certain substituents, such as the nitro group or halogens, deactivate the ring to which they are attached, and new substituents enter the unsubstituted ring. Thus, 4-chlorodiphenyl gives on nitration a mixture consisting of 4-chloro-2'-nitro- and 4-chloro-4'-nitrodiphenyl. Substituted phenyl groups also are *ortho-para* directing, regardless of the position of the substituent. The substituted phenyl group C_6H_4X behaves as a more powerful directive group than the phenyl group, if X is an activating *ortho-para* directing group such as NH_2 , OH or CH_3 , and less powerful if X is a deactivating *meta* directing substituent such as NO_2 . Only when the aromatic ring undergoing substitution contains another substituent group, more powerful in its directive influence than the substituted phenyl group linked to it, can substitution in the *meta* position take place. In 2- and 4-acetamidodiphenyl 5- and 3-substitution can occur, as well as substitution at position 3'.

4-Hydroxydiphenyl is substituted first in position 3, but its methyl ether gives, in addition, some 4'-substituted product, and in the case of the acyl derivatives, the 4'-substituted derivative forms the principal product. The three isomeric diphenylpyridines substitute largely in the *ortho* and *para* positions to the pyridyl group.

Internuclear directive effects have been detected with certainty in phenyl-

pyridines, though they are not strongly marked, but such effects are absent in homocyclic systems such as diphenyl and azobenzene.

Substituents enter the *naphthalene* molecule in the cold almost exclusively at the α - or 1-position. Substitution is often preceded by a 1-4-addition; chlorine, for example, gives a dichloride which, on warming, loses hydrochloric acid to form α -chloronaphthalene. A second substituent enters the ring to which the first substituent is attached, providing the first substituent is of an activating polar character, such as OH, NH₂, or CH₃; otherwise the second substituent enters the unsubstituted ring.

Within a single ring of *naphthalene* the ordinary ortho-para directive influence of substituents seems to be operative. An amino or hydroxyl group in the 1-position will promote substitution in both 2- and 4-positions; the same groups in the 2-position will only promote substitution in the adjacent 1-position and not in the 3-position.

When substitution occurs in both rings, the substituents tend to occupy the α - rather than the β -position, regardless of what the polar nature of the first substituent may be. In the disubstitution product, the 1,5-isomer is the principal constituent, with some 1,8- product. Such substitution is promoted equally by the groups OH, NH₂, Cl, Br and CH₃, which are *ortho-para* directing and by NO₂ and COOH, which are *meta* directing in benzene. When an *ortho-para* directing group occupies the 2-position, the 6-position may be the point of attachment of a second substituent. Thus, the sulfonic group enters the 6-position on sulfonation of β -naphthol and β -naphthylamine.

In β -naphthol and β -naphthylamine, the 1-position exhibits functions normally associated with the *ortho* position of a phenol or an aromatic amine. A diazo compound couples at position 1 on reaction with β -naphthol. In α -naphthol the 4-position is the preferred point of attack. The 6-position in β -naphthol and analogous compounds is the favored point of secondary attack. Nitro and sulfo groups in α -position promote substitution in positions 5 and 8, preferably the latter.

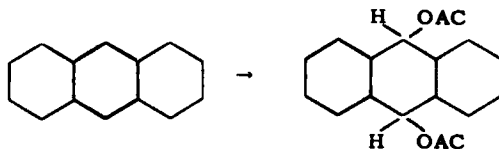
If one ring of the naphthalene nucleus carries a meta-directing group, a substituent tends to enter the other ring, preferentially at the more reactive α -position.

Substituents enter the aromatic nucleus of *acenaphthene*. Halogenation, nitration and sulfonation under normal conditions give monosubstituted derivatives, with the substituent entering position 3. The substituent enters position 1 when nitration is carried out with benzoyl nitrate, and when sulfonation is carried out with chlorosulfonic acid. 1-Nitroacenaphthene undergoes molecular rearrangement to the isomeric 3-nitro compound when heated in glacial acetic acid containing some mineral acid.¹⁴³

Sulfonation of *anthracene* gives α - and β -sulfonic acids. Sulfonation at low temperatures appears to favor the formation of the α -sulfonic acid, while at higher temperatures a greater proportion of the β -acid is obtained.¹³¹

The nitration of anthracene proceeds in an abnormal manner;¹³¹ a dihydroanthranol

appears to be the initial product, and is obtained in the form of its acetate when the nitration is carried out in acetic acid solution:



In alcoholic solution the ethyl ether, and in nitric acid, the nitrate is formed; nitration in acetic anhydride gives 9-nitroanthracene.

Halogenation of *phenanthrene* gives the 10-halo compound, presumably through the intermediate formation of 9,10-dihalo addition compound.¹⁴⁴ Nitration in glacial acetic gives principally the 10-nitro product with small amounts of 4- and 2-nitro derivatives. The result of sulfonation is dependent on the temperature of the reaction, the 10-sulfonic derivative being formed at 95 to 100°, and the 2- and 3-sulfonic derivatives at 120 to 130°.¹⁴⁵

Single substituents enter the *chrysene* nucleus at position 2; disubstitution gives the symmetrical 2,8-derivatives.

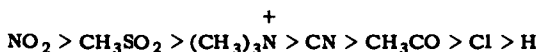
Activating Influence of Substituents

The mobility, or reactivity of halogen atoms and other negative substituents in an aromatic compound may be influenced to a marked degree by other substituents in the molecule. The carboxyl, cyano, formyl, acyl and sulfonic groups exert such an activating influence; an especially marked influence is exerted by nitro groups. It has been observed that groups which are activated by substituents in *ortho* or *para* position are themselves *meta* directing. There is also some evidence to show that *ortho* and *para* directing substituents exert an activating influence on substituents in *meta* position;¹⁴⁶ thus, one chlorine atom in 1,3,5-trichlorobenzene is more reactive than chlorine atoms in the isomeric trichlorobenzenes, while the nitro group in 1,3,5-trinitrobenzene is the least reactive of those in the three isomeric trinitrobenzenes.¹⁴⁷ The nitro group in 4-nitro-2-chlorobenzaldehyde is also activated by the chlorine in meta position and may be replaced with the methoxy group by reaction with sodium methoxide.¹⁴⁸ It has been observed that all activating negative groups have a characteristic in common; they all contain polyvalent elements with multiple

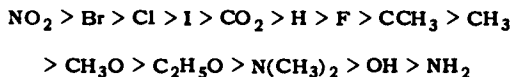
bonds, as in the groups $\text{--}\overset{\text{O}}{\parallel}\text{N}=\text{O}$, $\text{--}\text{C}\equiv\text{N}$, $\text{--}\overset{\text{O}}{\parallel}\text{C}$. The reactivity of the methyl

group in α -picoline has been ascribed to the potential pentavalence of the nuclear nitrogen.

The activating influence of substituents in the 4-position in 1-chloro-2-nitrobenzene on the chlorine atom in the reaction with sodium methoxide has been assessed and found to be as follows in descending order:²⁶¹



The activating effect of groups in 4-position in 1-bromo-2-nitrobenzene on the halogen in the reaction with piperidine has also been assessed and found to be as follows, in descending order:²⁶²



The marked activating influence of *nitro* groups comes to evidence in certain halo nitro compounds. Halogens are activated by nitro groups in *ortho* and *para* positions. The effect is cumulative, so that the chlorine in picryl chloride is highly reactive. The activating influence of nitro groups is observed also with hydroxy compounds; thus, the hydroxy group in 2,4-dinitrophenol and 2,4,6-trinitrophenol is replaceable with chlorine by reaction with phosphorus pentachloride.¹⁴⁹ Similarly, the hydroxy group in picric acid may be replaced with chlorine by reaction with toluenesulfonyl chloride in the presence of diethylaniline. Toluenesulfonyl esters of *o*-nitrophenol and 2,4-dinitrophenol react with aniline and other primary amines to give nitroamines.¹⁵⁰ Nitro groups are also activated by other nitro groups attached to the *ortho* and *para* positions in the aromatic nucleus. One nitro group in 1,2-dinitrobenzene may be removed by reaction with aqueous alkali, giving the alkali metal salt of *o*-nitrophenol; reaction with alcoholic ammonia results in the formation of *o*-nitroaniline.¹⁵¹ 2,3-Dinitrotoluene, reacting with alcoholic ammonia, gives *m*-nitro-*o*-toluidine, while 2,5-dinitrotoluene gives 5-nitro-*o*-toluidine as the principal product.¹⁵² 1,2,3-Trinitrobenzene reacts rapidly with sodium methoxide to give 2,6-dinitroanisole; 1,2,4-trinitrobenzene gives 2,4-dinitroanisole.¹⁵³

In the more complex polynitrated aromatic compounds the activating influence of the nitro groups may be enhanced or diminished by other groups attached to the nucleus. The active groups in a number of polynitro compounds are indicated below:

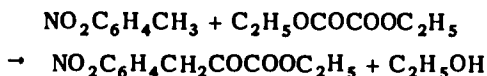
Compound	Active Group
1,4-dichloro-2,3-dinitrobenzene	2-nitro ¹⁵⁴
1-chloro-3,4,6-trinitrobenzene	chlorine, 2-nitro ¹⁵⁵
1-chloro-2,3,5-trinitrobenzene	2-nitro ¹⁵⁵
1-chloro-2,3,4-trinitrobenzene	chlorine, 3-nitro ¹⁵⁵
1-chloro-3,4-dinitrobenzene	3-nitro ¹⁵⁶
1-bromo-3,4,6-trinitrobenzene	bromine, 3-nitro ¹⁵⁷
2-chloro-4,5-dinitrotoluene	5-nitro ¹⁵⁸
2-chloro-4,6-dinitrotoluene	6-nitro ¹⁵⁸
2,3-dinitrotoluene	2-nitro ¹⁵⁹
2-nitro-3-chlorotoluene	chlorine ¹⁵⁹
2,5-dinitrotoluene	2-nitro ¹⁵²

Steric factors as well as the effect of the substituents appear to determine the point of attack.¹⁶⁰

Nitro groups also activate hydrogen atoms in the aromatic ring in *ortho* and

para positions. Thus, *m*-dinitrobenzene reacts with hydroxylamine in the presence of alcoholic potassium ethoxide forming 2,4-dinitroaniline and 2,4-dinitro-*m*-phenylenediamine.¹⁶¹ Similarly, *m*-dinitrobenzene, heated with an alcoholic solution of potassium cyanide, is converted first to 2,6-dinitrobenzonitrile, then to 2-nitro-6-methoxybenzonitrile. 2,4-Dinitrochlorobenzene yields successively 2,4-dinitro-3-cyanochlorobenzene and 2-nitro-3-cyano-4-methoxychlorobenzene.

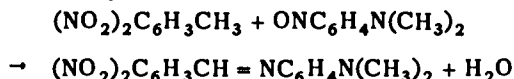
Nitro groups are also capable of activating methyl groups in *ortho* or *para* position. Thus, *o*- and *p*-nitrotoluene, condensing with oxalic ester in the presence of potassium ethoxide, give nitrophenylpyruvic ester.¹⁶²



2,4-Dinitrotoluene reacts with benzaldehyde in the presence of secondary amines to form 2,4-dinitrostilbene:¹⁶³



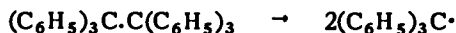
2,4-Dinitrotoluene condenses with *p*-nitrosodimethylaniline to form dinitrobenzylidene-*p*-aminodimethylaniline:¹⁶⁴



The reaction proceeds well, and since the product may be readily hydrolyzed by acid to 2,4-dinitrobenzaldehyde, it offers a convenient method for the preparation of this compound.

Free Radicals¹⁶⁵

Hexaphenylethane and other hexaarylethanes tend to dissociate in solution to triarylmethyls which show properties that mark them as *free radicals*:

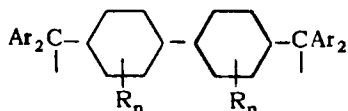


These are *complexes of abnormal valency possessing additive properties and devoid of an electric charge*, differing in this respect from free ions.

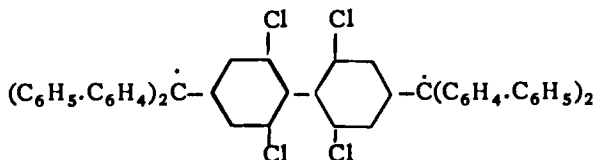
While the tendency toward dissociation into free radicals is especially marked in triaryl ethanes, the property of generating free radicals is shared, in varying degrees, by other types of organic compounds. Free radicals appear, in effect, to play an important part in many reactions, especially those catalyzed by light and by peroxides.

The disruption of the C—C linkage in hexaphenylethane often results from the ionization of the molecule, which occurs, for example, in liquid sulfur dioxide solution. Dissociation takes place in ionizing as well as non-ionizing solvents such as benzene and naphthalene.

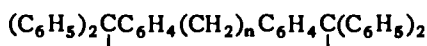
Compounds of the type



in which substituents in the diphenyl rings make the formation of quinoid structure impossible, are capable of forming free biradicals¹⁶⁶ such as



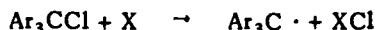
Meta-substituted diphenyls and compounds of the general type



also can give rise to biradicals for the same reason.

Methods of Preparation

Radicals of triarylmethyl series may be obtained readily by *Gomberg's method*, which consists in treating triarylmethyl halides with a metal:



Silver powder and mercury may be employed with satisfactory results, since they react readily at room temperature and form halides which are easily removed by filtration. Zinc and copper have also been employed for the purpose.¹⁵⁷ Ether, benzene, petroleum ether, carbon disulfide and ethyl acetate have been used as solvents. It is important that the solvent be quite free from moisture, dissolved oxygen or traces of acids. Light tends to destroy radicals and should be excluded. The procedure is to shake the mixture of the reagents at room temperature and to filter off the inorganic halides without exposing the liquid to the air.¹⁶⁸

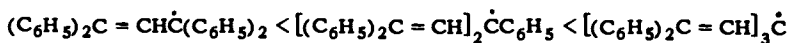
The halogen atom from triarylmethyl halides can also be removed by use of Grignard reagents or metallic alkyls. Metallic magnesium cannot be used, since it reacts with aryl halides to form an organomagnesium halide Ar_3CMgX .

Triarylmethyl radicals may be obtained through the reduction of triarylmethyl chlorides or triarylcabinols in solution in concentrated hydrochloric or sulfuric acid with powerful reducing agents which undergo a unit valency change, such as vanadous, titanous or chromous chlorides.¹⁶⁹

In the alkyl hexaarylethane series, $(p\text{-Alk-C}_6\text{H}_4)_3C \cdot C(C_6\text{H}_4\text{-}p\text{-Alk})_3$, the extent of dissociation to radicals increases with increase in the size of the alkyl substituent.¹⁷⁰ The replacement of one phenyl in triphenylmethyl with a phenoxy group decreases the stability of the radical. Methoxy groups in *ortho* and *para* position in two phenyl groups have a more marked effect on radical stability than when present in the same phenyl group.¹⁷¹ Tribiphenylmethyl $(C_6H_5 \cdot C_6H_4)_3C$ is of a dark violet color even in the solid state, indicative of radical character, and in solution exists only in the form of the free radical. On the other hand, bis-(diphenylenediphenyl)ethane does not dissociate into radicals. Diphenylenediphenylethane, tetraphenylbisdiphenylethane and diphenyltetraabiphenylethane occupy an intermediate position between these two extremes.¹⁷² Triphenylmethyl radicals with nitro groups attached to all three benzene nuclei are also quite stable.²⁴⁸ Large groups such as the crysly and the phenanthryl

groups increase radical stability.¹⁷³ Pentaphenylcyclopentadienyl has the character of a radical.²⁴⁹

The dissociation of compounds such as $(\text{C}_6\text{H}_5)_2\text{C}(\text{CH}_3) \cdot \text{C}(\text{CH}_3)(\text{C}_6\text{H}_5)_2$ may be inferred only from the reactions which they undergo. There are indications that sym-tetra- $(\beta, \beta$ -diphenylvinyl)ethane dissociates into radicals.¹⁷⁴ Other compounds of this class also give rise to radicals by dissociation. The stability of some of these radicals is in the order shown below:

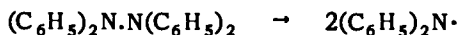


Free radicals are not formed if the vinyl group is capable of undergoing the allylic rearrangement.¹⁷⁵

Phenyl radicals have been produced through the photo-dissociation of benzene.¹⁷⁶

Radicals with Nitrogen Atoms

Aromatic groups attached to nitrogen may induce radical forming ability to the complex. Tetraphenylhydrazine, for example, is capable of dissociating into a radical:¹⁷⁷



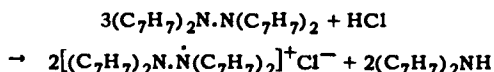
It should be pointed out, however, that tetraphenylhydrazine undergoes disproportionation at the temperatures necessary for dissociation, giving diphenylamine and diphenyldihydrophenazine.

Tetra-p-tolylhydrazine in solution in anhydrous ether, treated with iodine and silver perchlorate, gives a dark violet crystalline salt which apparently possesses the character of a radical,¹⁷⁸



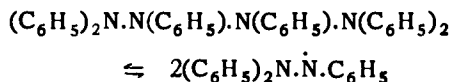
Tri-*p*-tolylamine in solution in dry benzene, treated with lead peroxide in the presence of picric acid, gives a salt of similar character.¹⁷⁹ Double salts of mercury, aluminum, antimony and phosphorus halides have been prepared from the perchlorate.

Radical-cation complexes are formed only from aromatic tertiary amines and hydrazines. These compounds do not form normal salts with acids. Tetraarylhydrazines give rise to hydrazinium salts assuming a radical character in acid solution, without the use of an oxidizing agent:



Meta directing groups, such as NO_2 , decrease the ease of dissociation, while *para* directing groups enhance the ability of the compound to form radicals.

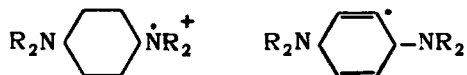
Triphenylhydrazine in solution in anhydrous ether, shaken with lead peroxide at room temperature, gives a deep blue solution containing the radical triphenylhydrazyl:¹⁸⁰



The reaction product of *asym*-diphenylhydrazine and picryl chloride, treated in anhydrous ethereal solution with lead peroxide, gives the radical α,α -diphenyl- β -trinitrophenylhydrazyl,¹⁸¹ $(\text{C}_6\text{H}_5)_2\text{N}\cdot\dot{\text{N}}\text{C}_6\text{H}_2(\text{NO}_2)_3$.

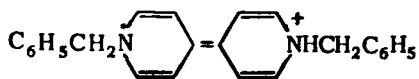
Oxidation of diphenylhydroxylamine in anhydrous ethereal solution with silver oxide results in the formation of a deep red solution containing the radical diphenylnitric oxide,¹⁸² $(\text{C}_6\text{H}_5)_2\dot{\text{N}}\text{O}$. The radical can be isolated from the solution by freezing.

Oxidation of certain aromatic diamines with bromine results in the formation of stable salts having a radical character, and known as Wurster's salts:¹⁸³



The important requirement for the formation of stable radical salts is that a sufficiently high molecular symmetry be present for the occurrence of resonance throughout the whole molecule. The benzene ring, the *para* nitrogen and the four attached groups must all lie in one plane.

Tetrahydro- γ,γ' -dipyridyl derivatives give on oxidation deeply colored very reactive salts. $\text{N,N'$ -dibenzyltetrahydro- γ,γ' -dipyridyl gives two hydriodides, $\text{C}_{24}\text{H}_{22}\text{N}_2\cdot\text{HI}$, $\text{C}_{24}\text{H}_{22}\text{N}_2\cdot 2\text{HI}$.¹⁸⁴ The subiodide is a free semiquinoid radical,



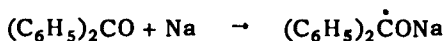
Radicals with Oxygen Atoms

Oxidation of phenanthraquinol monomethyl or monoethyl ether with alkaline potassium ferricyanide results in the formation of nearly colorless peroxides, which yield greenish yellow solutions that darken on standing, and contain free radicals.¹⁸⁵ A radical is also obtained from 9-chloro-10-hydroxyphenanthrene, the peroxide in this case dissociating to the extent of 69%.¹⁸⁶

Alkyl Radicals

The free *methyl* radical can be obtained by heating azomethane to about 400° ,¹⁸⁷ or by heating lead tetramethyl in a rapid stream of hydrogen or nitrogen under low pressure in a quartz tube.

In the reaction of sodium with vapors of methyl chloride, the carbon to chlorine covalent link is broken with the formation, initially, of a chlorine anion and a methyl radical. The reaction of metallic sodium with many other types of compounds, such as aromatic ketones, olefins and nitriles also results in radical formation:



The thermal decomposition of many organic compounds, such as paraffin hydrocarbons, ethers, alcohols, aldehydes, ketones and amines results in the formation of the simple alkyl radicals methyl, ethyl, etc., although radical formation comprises a small proportion of the total reaction.¹⁸⁸ The photochemical decomposition of molecules of

various types leads to the formation of free radicals of short life.¹⁸⁹ Free radicals are also formed from gases, such as methane, when they are subjected to an electric discharge.

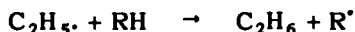
Ethyl radicals may be prepared by the thermal decomposition of tetraethyl lead. *n-Propyl radicals* have been produced by irradiating n-propyl ketone.¹⁹⁰

Reactions of Free Radicals

Free radicals combine readily with metals and with halogens. The free methyl radical combines directly with lead, antimony, tellurium and zinc. Reaction velocity measurements have shown that the radical unites instantly with elements without requiring any energy of activation. The triphenylmethyl radical reacts instantaneously with halogens, reaction proceeding readily with chlorine and bromine even at -10° .¹⁹¹ The addition of iodine to triphenylmethyl proceeds quantitatively at 0° in carbon disulfide solution.¹⁹² The halogen in triphenylhalomethanes is bound very loosely. In many respects these halo compounds behave like metallic salts, their solutions in pyridine, acetone and sulfurous acid conducting the electric current.¹⁹³ The C-F linkage in free radicals appears to be less firm than that in aliphatic compounds, although the opposite is apparently true of the C-Br linkage. The triphenylmethyl radical combines with NO and NO₂ forming colorless triphenylnitrosomethane and triphenylnitromethane, which decompose into their components on heating.¹⁹⁴

Addition of oxygen to hydrocarbon radicals takes place very readily. Solutions of triphenylmethyl absorb oxygen from the air to form triphenylmethyl peroxide, $(\text{C}_6\text{H}_5)_3\text{C} \cdot \text{O} \cdot \text{O} \cdot \text{C}(\text{C}_6\text{H}_5)_3$.¹⁹⁵ Other triarylmethyl radicals are also converted to peroxides by atmospheric oxygen. These peroxides are difficultly soluble and chemically inert.¹⁹⁶ Triphenylmethyl peroxide may be crystallized from carbon disulfide. Boiling a xylene solution of the peroxide under reflux under a carbon dioxide atmosphere results in the formation of the diphenyl ether of benzpinacone, $(\text{C}_6\text{H}_5)_2\text{C}(\text{OC}_6\text{H}_5)\text{C}(\text{OC}_6\text{H}_5)(\text{C}_6\text{H}_5)_2$, which is capable of dissociating to the radical $(\text{C}_6\text{H}_5)_2\dot{\text{C}}\text{OC}_6\text{H}_5$.¹⁹⁷

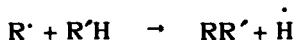
A radical, reacting with a saturated aliphatic hydrocarbon, yields a new radical:



An addition reaction takes place with unsaturated hydrocarbons again yielding a free radical:



Ethyl radicals apparently do not react with benzene or naphthalene, although aromatic radicals react with aromatic hydrocarbons replacing a hydrogen atom:



Cases are also known where both a replacement of a hydrogen atom and hydrocarbon radical formation take place simultaneously.

In the reaction of radicals with aromatic compounds, the rules of aromatic

substitution do not hold. For example, in the reaction of 4-nitrosoacetamidodiphenyl with chloro- and bromobenzene, substitution takes place at all three positions in the halobenzene nucleus.¹⁹⁸

Radicals of the general formula $(p\text{-RC}_6\text{H}_4)_3\dot{\text{C}}$, in which R = C_2H_5 , n-propyl, isopropyl, sec-butyl, and isobutyl, undergo disproportionation, the ethylene compound, for example, giving $(\text{C}_2\text{H}_5\text{C}_6\text{H}_4)_3\text{CH}$ and $(\text{C}_2\text{H}_5\text{C}_6\text{H}_4)_2\text{C}=\text{C}=\text{C}_6\text{H}_4=\text{CHCH}_3$.¹⁹⁹ The disproportionation reaction is confined to those *p*-alkyltriphenylmethyls in which the alkyl group has at least one hydrogen atom attached to the carbon atom adjacent to the ring. The rates of disproportionation decrease with increase in the size of the alkyl group.

Free radicals are, as has been pointed out, electrically neutral, and their solutions are paramagnetic. They form easily dissociable addition complexes with solvents such as chloroform, benzene, cyclohexane and heptane, and are thereby stabilized to some extent.²⁰⁰

The quantitative reaction between oxygen and a free radical has been utilized as a *method of analysis* for free radicals, the quantity of insoluble peroxide formed being determined for the purpose.

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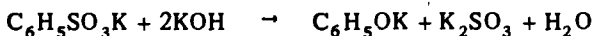
CHAPTER 23

PHENOLS AND QUINONES

PHENOLS

Phenols by the Caustic Fusion Method

Aromatic sulfonic acids fused with caustic give the alkali metal salt of phenols:



This reaction forms the basis of the most important method of preparation of phenols.

The fusion is carried out in open vessels. Yields in the neighborhood of 96% are obtained with a 15% excess of sodium hydroxide, a fusion temperature of 350° and a heating time of 15 minutes. Yields are nearly as good at 300° providing a 50% excess of caustic is used and period of heating is extended to 30 minutes. A greater proportion of by-products are formed at the higher temperature if only a slight excess of caustic is used. In some instances the use of potassium hydroxide is preferable because of its lower melting point and greater reactivity. Mixtures of sodium and potassium hydroxides are often used in order to lower the fusion temperature. A small amount of water is added to the caustic in the industrial preparation of certain phenols such as resorcinol and naphthol. The method is suitable for the preparation of dihydric phenols from phenol-sulfonic acids, although reaction with phenol-*p*-sulfonic acid proceeds at temperatures in excess of 320° and results in the formation of complex products. The yield is improved considerably when the barium salt of the sulfonic acid is fused at 290 to 310° with a mixture of sodium and potassium hydroxides.²²⁸

Alkali fusion results in some cases in the partial or complete replacement of the sulfonic group with hydrogen. Cresolsulfonic acid, for example, yields cresol when fused with potassium hydroxide, and 2,3-dihydroxynaphthalene-6-sulfonic acid gives 2,3-dihydroxynaphthalene. The sulfite resulting from the reaction can exert a reducing action on groups susceptible of reduction; for this reason alkali fusion of nitrosulfonic acids can seldom be carried out with success.

The reverse effect, namely the oxidation of the expected phenolic body, is also observed occasionally, as in the fusion of β -hydroxyanthraquinone, which results in the formation of alizarin.²²⁹

In the alkali fusion of naphthalenesulfonic acid, nuclear hydroxylation may take place.

Alkali fusion may also bring about the partial breakdown of the molecule of the aromatic sulfonic acid. Anthraquinonesulfonic acid, for example, is converted to hydroxybenzoic acid.²³⁰ Degradation is observed also with naphthalene-1,3-disulfonic acid and 1,3,5-, 1,3,6-, 1,3,7- and 1,3,8-trisulfonic acids.²³¹

If alkyl groups are present in the benzene ring, by-products are increased.

The alkyl groups in some compounds are oxidized to carboxyl, and the consequent reduction of solubility in the fused caustic may seriously interfere with the reaction.

Ortho- and *para*-toluenesulfonic acids are readily converted to cresols by fusion with potassium hydroxide.²³² Sodium *p*-toluenesulfonate is not appreciably soluble in fused sodium hydroxide and therefore no reaction takes place with sodium hydroxide. *Mesitylenesulfonic acid* fused at 285 to 298° with three parts of potassium hydroxide gives chiefly mesitol, but when heated at 240 to 250° for a longer period, it is largely converted to 2-hydroxy-3,5-dimethylbenzoic acid.²³³ The reason for this appears to be the fact that at 240 to 250°, the mixture remains homogeneous, whereas at the higher temperature, the potassium salt of mesitol separates as a second layer at the top, and thus escapes oxidation. Carvacrol is obtained in 70% yield by heating one-tenth molecular proportion of 2,4-*isopropylmethylphenylsulfonic acid* with two molecular proportions of sodium hydroxide at 350 to 360° for six hours.²³⁴ Thymol has been prepared in 59% yield by fusing 3,6-*isopropylmethylphenylsulfonic acid* with two or three times its weight of potassium hydroxide at 350° for 30 minutes.²³⁵ Sodium hydroxide gives poor results in this case.

The presence of *hydroxyl* or *amino* groups *ortho* or *para* to the sulfonic group causes a great decrease in the reactivity of the latter. Replacement of the sulfo group occurs with difficulty and is accompanied by molecular rearrangements or complete decomposition of the molecule. A *nitro* group also interferes in the reaction, since it acts oxidatively and causes the breakdown of the molecule.²³⁶ If a methyl group is present in the molecule in the *para* position to the nitro group, as in 4-nitrotoluene-2-sulfonic acid, alkali fusion results in the formation of dyestuffs related to stilbene.²³⁷

Catechol is formed in small yield when *o*-hydroxybenzenesulfonic acid is fused at 330 to 360° with sodium or potassium hydroxide.²³⁸ Fusion of *p*-hydroxybenzenesulfonic acid produced no appreciable amount of hydroquinone. Resorcinol is formed when 3-hydroxybenzenesulfonic acid is fused with caustic.²³⁹ *m*-Benzenedisulfonic acid is converted to resorcinol when fused with an excess of sodium hydroxide at or above 270°.²⁴⁰ If the usual fusion apparatus is employed, seven molecular proportions of alkali are required to one of sodium benzenedisulfonate. The proportion may be reduced to five of caustic to one of sulfonic acid if the vessel is provided with a stirrer. Best results are obtained by holding the temperature initially at 300 to 310°, then raising it to 318 to 320°.²⁴¹ *m*-Xylene-2,4-disulfonylchloride, fused with potassium hydroxide, gives the corresponding dimethylresorcinol.²⁴² The 6-halo derivatives of the sulfonic acid are also converted to the corresponding halodimethylresorcinols.²⁴³

The first sulfonic group in *sym*-benzenetrisulfonic acid may be replaced by heating with caustic at 150°; the second sulfonic group is replaced at 240 to 260°.²⁴⁴ Best results are obtained when the sulfonate is fused with six times its weight of sodium hydroxide.

Sulfanilic acid, heated with fused potassium hydroxide at 350 to 355°, gives *p*-hydroxybenzenesulfonic acid in 77% yield.²⁴⁵ 2-Nitroanilinesulfonic acid is similarly converted to *p*-hydroxybenzenesulfonic acid.²⁴⁶

Sulfobenzoic acids $\text{HSO}_3\text{C}_6\text{H}_4\text{COOH}$ give the corresponding hydroxybenzoic acids in 90 to 100% yield when fused with potassium hydroxide.²⁴⁷ Alkylated sulfobenzoic acids react in a normal manner. 2,4-Dimethyl-5-sulfo- and 3,5-dimethylsulfo derivatives form an exception and give the corresponding cresylic acids by replacement of the sulfonic group with hydrogen.²⁴⁸ 4-Sulfo-3-hydroxy- and 3-sulfo-4-hydroxybenzoic acids yield

the dihydroxy acids, although a second acid is also obtained from the former.²⁴⁹ Both sulfonic groups in 3,5-disulfobenzoic²⁵⁰ and 2,4-disulfobenzoic²⁵¹ acids may be replaced with hydroxyl groups without loss of the carboxyl group.²⁵⁰

The sulfonic group in aromatic sulfonic acids with a carbonyl group in a side chain is first replaced with a hydroxyl group on fusion with caustic. Further heating causes the oxidation of the side chain to a carboxyl group.²⁵²

Naphthalene α - and β -sulfonic acids are readily converted to the corresponding naphthols by fusion with three parts of sodium or potassium hydroxide at 300 to 320°. ²⁵³ Naphthalene is a by-product of the reaction. Among the sulfonated derivatives of naphthalene, α -sulfonic acids are in general more reactive than the β -acids.²⁵⁴

Hydroxynaphthalenemonosulfonic acids may be converted by the corresponding dihydroxy compounds by fusion with caustic.²⁵⁵ For β -naphtholsulfonic acids a much higher temperature is required for the replacement of the 6-sulfonic group than for the 7-sulfonic group. Conversion of *naphthalenedisulfonic acids* to the dihydroxy compounds can also be effected by caustic fusion.²⁵⁶ It is generally possible to replace only one sulfonic group with a hydroxyl group.²⁵⁷

1,6-Dihydroxynaphthalene-3-sulfonic acid yields the trihydroxy compound below 270°. ²⁵⁸ One, two or three sulfonic groups in naphthalenetrisulfonic acids are replaceable with hydroxyl by treatment with caustic and subsequent decomposition of the resulting sodium salts with acid. Breakdown to the sodium salt of hydroxytoluic acid occurs if two of the sulfonic groups are in *meta* position to each other.²⁵⁹

Many *aminonaphthalenedisulfonic acids* yield the sodium salts of aminonaphtholsulfonic acids by caustic fusion.²⁶⁰ A large number of these compounds are dye intermediates. Aminonaphthalenesulfonic acids generally show little tendency to exchange amino groups for hydroxyl in caustic fusion reactions. An amino group in the *para* position to the sulfonic group is replaceable with a hydroxyl group; an amino group in the *peri* position may also be thus replaced.

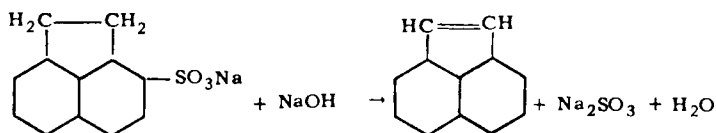
Sulfonated naphthalenecarboxylic acids are converted to hydroxy compounds without loss of the carboxyl group.²⁶¹ The same holds true of hydroxy sulfo carboxylic and sulfo dicarboxylic acids, although 2-sulfo-1,8-naphthoic acid is converted to 7-hydroxynaphthoic acid by caustic fusion.²⁶²

Anthracene-1- and -2-sulfonic acids are converted to the sodium salt of the corresponding hydroxy compounds by fusion with sodium hydroxide at 180 to 300°. ²⁶³ The sulfonic groups in anthracenedisulfonic acids may be replaced in steps, first yielding a hydroxy sulfonic acid, then a dihydroxyanthracene.²⁶⁴

Sulfonated anthraquinones are converted to hydroxy compounds at a lower temperature than anthracene derivatives. Anthraquinone-2-sulfonic acid is converted to alizarin on fusion with sodium hydroxide, although conversion is not complete unless the fusion is carried out in the presence of an oxidizing agent such as potassium nitrate or chlorate.²⁶⁵ Fusion of *anthraquinone-2,6- or 2,7-disulfonic acid* with sodium hydroxide gives little of the dihydroxy derivative, and the main product is a trihydroxyanthraquinone. The 2,6-disulfonic acid gives 1,2,6-trihydroxyanthraquinone (flavopurpurin).²⁶⁶

The potassium or barium salt of *phenathrene-2- or -3-sulfonic acids* give 72% yield of the potassium salt of the phenanthrol when fused with three parts by weight of potassium hydroxide at 300 to 325°. ²⁶⁷

Acenaphthene-3-sulfonic acid behaves abnormally on fusion with caustic and is converted to acenaphthylene.²⁶⁸



Halogenated aryl sulfonic acids and phenols exchange their halogen for an -OK group when fused with potassium hydroxide. Intramolecular rearrangements take place occasionally in this reaction. For example, all three halobenzene-sulfonic acids yield the potassium salt of *meta*-dihydroxybenzene when fused with potassium hydroxide.

Phenols by Reaction with Aqueous Caustic

Replacement of sulfonic groups in aromatic sulfonic acids may be brought about by heating the compounds in an autoclave with an aqueous solution of caustic. This method offers the advantage that the reaction can be controlled more accurately. Furthermore, since the reaction is carried out in a closed vessel, the deleterious action of the oxygen of the air is eliminated. For these reasons purer products and better yields are obtained, particularly where sensitive substances are involved.

β -Naphthalenesulfonic acid is converted to *β -naphthol* by heating with 1% caustic at 300° under pressure. Phenol is formed as the principal product when *o*- and *p*-phenolsulfonic acids are heated under pressure with aqueous caustic.

The sulfonic group in *anthraquinonesulfonic acids* may be replaced with a hydroxyl group by heating the compound with an aqueous solution or suspension of an alkaline earth hydroxide. Anthraquinone *α* -sulfonic acids are converted to hydroxyanthraquinones by heating at 180 to 200° with milk of lime.²⁶⁹

The reaction of di- and polysulfonic acids may be carried out stepwise. Thus, the reaction of benzene-*m*-disulfonic acid under mild conditions results in the formation of phenol-*m*-sulfonic acid, while resorcinol is formed under more vigorous conditions.²⁷⁰ In the naphthaleneseries, the sulfo group in *α* -position is attacked first. The technically important 2,5,7-, 2,8,6-, and 1,8,4-aminonaphthol-sulfonic acids and 1,8,3,6-, 1,8,4,6-, and 1,8,2,4-aminonaphthol disulfonic acids are produced from the corresponding naphthyamine di- and trisulfonic acids by partial replacement of the sulfonic groups with hydroxyl groups.

Halogenated benzene derivatives react with dilute alkalis at elevated temperatures to form phenols.¹ The reaction proceeds at temperatures in excess of 300° under 200 atm pressure. Base metal catalysts accelerate the reaction. Direct exchange of a halogen atom with a hydroxyl group by reaction with water is possible with certain aromatic compounds in the presence of special catalysts such as a mixture of iron-free aluminum oxide and copper or cobalt, or porous materials like pumice or chalk impregnated with cupric chloride.² Nitro groups in *ortho* or *para* position greatly facilitate the replacement of halogens with hydroxyl groups, simple heating with aqueous caustic and subsequent acidification being sufficient to obtain the phenol.²⁷¹ Trinitrochlorobenzene reacts readily with water to form the corresponding phenol.

The acetamino group in *4-nitroacetanilide-3-sulfonic acid* is eliminated on heating at 100° with aqueous alkali.²⁷² The amino group in aminonaphthalene-sulfonic acids is also often replaced on heating with aqueous caustic.

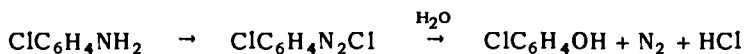
2-Hydroxynaphthalene-3,6-disulfonic acid heated with dilute alkali is converted to 2,3-dihydroxynaphthalene, one sulfonic group being replaced with

hydroxyl, the other with hydrogen.²⁷³ Other hydroxynaphthalene sulfonic acids react normally and yield dihydroxynaphthalene sulfonic acids.²⁷⁴

Anthraquinone-1-sulfonic acid is hydrolyzed by aqueous sodium carbonate at 200°. ²⁷⁵ Reaction with aqueous sodium hydroxide occurs at still lower temperatures. ²⁷⁶ Conversion to the hydroxy compound takes place by heating the sulfonic acid at 180 to 200° with aqueous calcium- or barium hydroxides without ring cleavage, oxidation or other side reactions. *Anthraquinone-2-sulfonic acid* is converted to the hydroxy compound by heating with 20% aqueous sodium hydroxide at 160–165°.

Phenols from Aromatic Amines

Phenols may be obtained from amino compounds by conversion to diazonium salts and subsequent heating with dilute sulfuric acid:

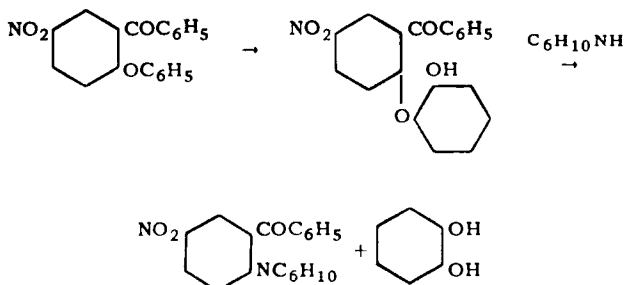


The conversion of aminophenols to dihydric phenols by the diazo reaction proceed poorly or does not proceed at all.³ The general subject of the replacement of diazo groups by the hydroxyl group is considered in Chapter 27 dealing with aromatic diazo compounds.

The amino group may be replaced with a hydroxyl group directly by boiling with aqueous alkalis, provided nitro groups are present in the aromatic nucleus at the *ortho* and *para* positions.

1,2,4,5-Tetrahydroxybenzene has been prepared by prolonged boiling of 3,4,6-triaminophenol with aqueous alkali; trihydroxyaminobenzene is first formed in the reaction and changes to tetrahydroxybenzene on longer boiling.

Phenol is formed through the oxidation of benzene with hydrogen peroxide or ozone. Dihydric phenols may be obtained through the oxidation of monohydric phenols with hydrogen peroxide or with persulfates (*Dakin oxidation*).⁴ Catechol derivatives are obtained along with other products by the hydroxylation of the cresols and 2,4-dimethylphenol in acetic acid with diacyl peroxides.²⁸⁸ Aryloxynitrobenzophenones undergo hydroxylation to hydroxyphenyl ethers when treated with sulfuric acid and hydrogen peroxide. It is possible that a xanthyllium sulfate forms as an intermediate. Fission of the ether with piperidine yields a catechol and a nitrobenzophenone;²⁸⁹



Di- and trihydroxybenzenes may be obtained by fusing phenol with potassium hydroxide.

Alkylation of Phenols

The introduction of alkyl groups into the nucleus of phenols by Friedel-Crafts method does not, as a rule, proceed smoothly,⁵ although reaction takes place satisfactorily with phenol ethers.

Alkylation of phenols may be effected by heating these compounds at 200° with an alcohol in the presence of zinc chloride.⁶ *p*-Isobutylphenol has been obtained by this method from phenol and isobutyl alcohol. Magnesium chloride or alkali metal acid sulfates may be substituted for zinc chloride.⁷ Alkyl ethers are formed simultaneously in the reaction. Phenyl methyl ether, $C_6H_5OCH_3$, is the sole product when methanol is used in the reaction with phenol.

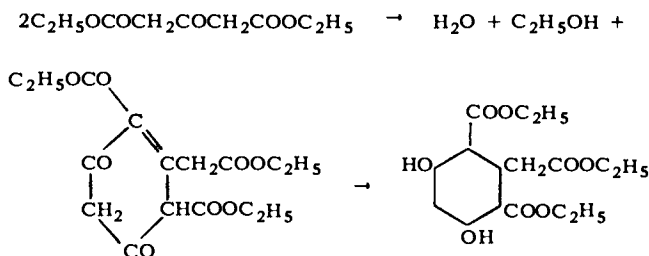
Alkyl phenols also result through the reaction of a phenol with unsaturated hydrocarbons in the presence of sulfuric acid, aluminum chloride or boron trifluoride.⁸ Propylene and *m*-cresol give the various isomers of isopropyl-*m*-cresol, together with the saturated phenol ether.

Alkylation of phenols with secondary butanol to dissecondary butylphenol has been accomplished in cold anhydrous hydrogen fluoride. The compound has been obtained in 73.8% yield.

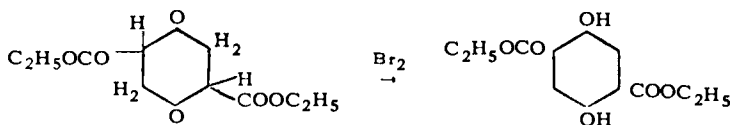
The condensation of phenolic compounds with formaldehyde under the influence of alkali metal hydroxides to phenolic methylol derivatives is known as the Lederer-Manasse reaction. This subject has been treated in Chapter 5.

Phenols from Aliphatic Ketones

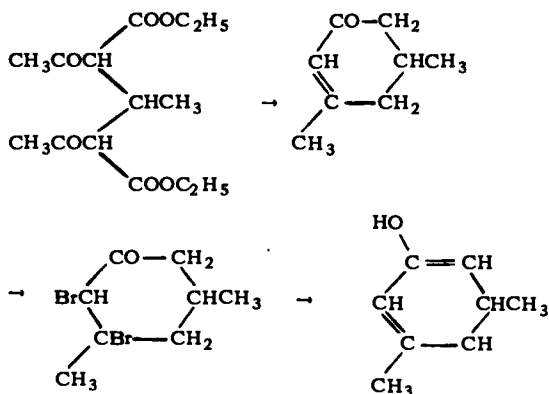
Certain phenolic compounds have been synthesized through the intramolecular condensation of aliphatic keto compounds. Dihydroxyphenylacetic dicarboxylic ester has been obtained, for example, from acetonedicarboxylic ester by heating in the presence of metallic sodium:



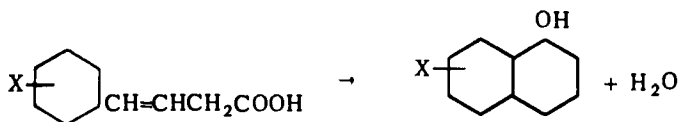
Dihydroxyterephthalic ester results on treating succinylsuccinic ester with bromine:



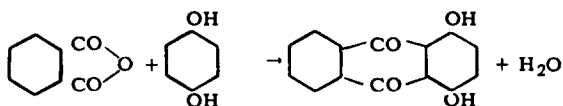
Xylenol has been made from ethylidenedi-acetoacetic ester by condensation to dimethylcyclohexanone, conversion of the latter to the dibromide and dehydrobromination of this:



Naphthols may be prepared by the methods employed for the preparation of phenols; they are easily obtained from naphthalene sulfonic acids by fusion with caustic, and from naphthylamines by diazotization followed by replacement of the diazo group with hydroxyl. Substituted α -naphthols have been prepared from substituted phenylisocrotonic acid by ring closure:⁹



The most satisfactory method for the preparation of quinizarin, i.e., 1,4-dihydroxyanthraquinone, involves the condensation of phthalic anhydride with hydroquinone in the presence of boric acid. The latter converts quinizarin into its boric ester and this prevents further reaction:



Behavior and Reactions of Phenols

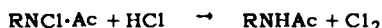
The hydroxyl group in phenols exhibits a distinctly acid character, and these compounds react with alkaline hydroxides forming salts; they do not, however, react with alkali metal carbonates, unless the acidic character of the phenolic hydroxyl group is enhanced by the presence in the nucleus of nitro groups or halogens.¹⁰ The acid character of trinitrophenol is so pronounced that the corresponding chloride reacts readily with water to form the phenol. Carbon dioxide precipitates phenols other than the nitrated and halophenols from the solutions of their alkali metal salts. The so-called cryptophenols or pseudophenols fail to dissolve in aqueous alkalis;¹¹ an example is presented by *p*-bromomethyl-tetrabromophenol, which exists also in the keto form. Hydroxy azo compounds also fail to dissolve in aqueous alkalis.

The hydrogen in the phenolic hydroxyl group may be replaced with an alkyl or

acyl group to form an ether or an ester, although, while such replacements may be effected directly with many aliphatic alcohols, phenolic ethers and esters may be prepared only by indirect methods. Naphthols differ in this respect from mononuclear phenols and may be directly etherified with alcohols.

The presence of the hydroxyl group in the aromatic nucleus facilitates the substitution of the nuclear hydrogen atoms by halogens and sulfonic and nitro groups. Increase in reactivity toward chlorine is, in fact, so pronounced that phenolic compounds cannot be successfully chlorinated by the usual methods.

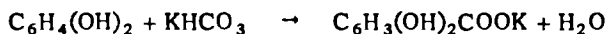
Chlorination may be effected satisfactorily by use of chloroamides in 0.02*N* hydrochloric acid solution, the chlorine utilized in the reaction originating in the reversible process



which proceeds from left to right in the presence of glacial acetic acid.¹² The amide chloride generally used for the purpose is 2,4-dichloroacetylchloranilide.

Dihydric phenols generally show a greater reactivity than monohydric phenols. For example, while monohydric phenols give monoalkylated derivatives when treated with alkylenes in the presence of a mixture of acetic and sulfuric acids, dihydric phenols yield disubstituted products when similarly treated.¹³ Many polyhydric phenols react with sugars in the presence of strong acids to form glucoside-like compounds.¹⁴

Dihydric phenols in which the hydroxyl groups are in *meta* position give dihydroxy carboxylic acids when heated with alkali metal carbonates under atmospheric pressure:



The reaction has been carried out successfully by heating dihydric phenols under pressure with potassium carbonate.¹⁵ Resorcinol and other *meta* dihydric phenols react to form fluoresceins when heated with phthalic anhydride.

Dihydric phenols may be converted into hydroaromatic keto chlorides by treatment with chlorine; the carbon ring of such ketones can then be readily ruptured. Such keto chlorides yield dihydroxy aldehydes, for example, when treated with chloroform and potassium hydroxide, and dihydroxy carboxylic acids when treated with carbon tetrachloride and caustic.

The halogen in *ortho* and *para*-halomethyl phenols shows unusual mobility; these compounds readily couple, for example, with phenols and tertiary amines of the dimethylaniline type, in the absence of condensing agents, to form compounds of the diphenylmethane series. A similar reactivity is shown also by the corresponding thiocyanates.¹⁶

The replacement of the hydroxyl group in phenols with chlorine by treatment with phosphorus pentachloride does not take place readily;¹⁷ phenol itself gives the ester $\text{C}_6\text{H}_5\text{OPCl}_4$ when treated with the reagent. The reaction proceeds more readily with nitrated phenols.

β -Naphthol readily yields β -halonaphthalene when treated with a phosphorus halide.¹⁸

Phenols are partially converted into thiophenols on heating with phosphorus pentasulfide.

Substitution of a phenolic hydroxyl group with an amino group generally requires drastic treatment, such as heating with the addition compounds of zinc chloride or calcium chloride with ammonia.¹⁹ Substitution takes place with relative ease in the case of nitroso phenols and naphthols.²⁰ Amino compounds are also obtained readily on heating the alkyl ethers of nitro phenols with alcoholic ammonia.

Phenols readily couple with diazonium compounds to form azo dyes; they also couple with benzotrichloride, $C_6H_5CCl_3$, giving yellow-red dyes, and with phthalic acid yielding phthaleins.

Phenols react with formaldehyde to form phenolic alcohols of the type of saligenin, $HOC_6H_4CH_2OH$. Resinous condensation products are formed in the presence of acids or alkalis which are more or less soluble in organic solvents.²¹

Reaction with malic acid in the presence of sulfuric acid results in the formation of coumarins, while with β -keto acids coumarins or chromones are formed depending on the keto acid used and on the phenol. Sulfuric acid invariably gives coumarins, but when phosphorus pentoxide is used as the condensing agent coumarins are obtained with resorcinol, phloroglucinol, pyrogallol and α -naphthol, and chromones are obtained with other phenols.²²

The sodium or potassium salts of phenols react with carbon dioxide to form phenol carboxylic acid, sodium salicylate resulting, for example, from the reaction of sodium phenoxide and carbon dioxide in aqueous solution. A similar reaction takes place between alkali phenolates and phosgene.

Phenols may be *reduced* to cyclic alcohols by conducting their vapors mixed with an excess of hydrogen over finely divided nickel heated to 215 to 230°. ²³ Phenols are reduced to the corresponding hydrocarbon when heated with zinc dust ²⁴ or with phosphorus trisulfide. ²⁵

Sodium amalgam causes the replacement of halogen atoms in phenols with hydrogen.

Polynitro phenols are only partially reduced to amino phenols by ammonium sulfide, but tin and hydrochloric acid bring about the complete reduction of the nitro groups.

Cresols and other alkyl phenols cannot be *oxidized* by the chromic acid mixture; oxidation of the alkyl groups takes place satisfactorily, however, when ethers of alkyl phenols are subjected to the action of the reagent. The readily accessible sulfuric and phosphoric esters may be conveniently used for the purpose; these esters are converted to the corresponding phenol ester carboxylic acids by alkaline permanganate, whereas the free phenols are completely destroyed by this reagent. ²⁶ In general, negative atoms or groups in *ortho* position hinder the oxidation of alkyl groups by acidic oxidizing agents and, conversely, facilitate oxidation by alkaline oxidizing agents. ²⁷

Methyl groups in cresols and xylenols are oxidized to carboxyl groups on fusion with alkali hydroxides in the presence of lead monoxide or dioxide. ²⁸

Phenol aldehydes are converted with difficulty into phenol carboxylic acids; conversion can be accomplished by fusion with alkalis. On oxidation with hydrogen peroxide *ortho* and *para* phenol aldehydes lose the carbonyl group and are converted to pyrocatechol and hydroquinone respectively. ²⁹

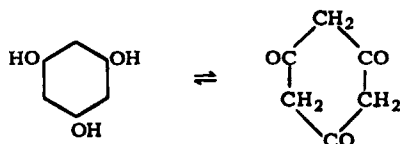
Di- and polyhydric phenols are distinguished by their reducing properties;

they are capable of reducing Fehlings solution and ammoniacal silver nitrate, and their alkaline solutions absorb oxygen from the air with the formation of dark colored products. This behavior is more marked with phenols in which the hydroxyl groups are in the *ortho* and *para* positions with respect to each other. *Para*-dihydroxybenzenes are readily oxidized to quinones, and these, in turn, are reconverted to *p*-dihydroxybenzenes by mild reducing agents such as sulfurous acid.

Naphthols in general behave like phenols, although the hydroxyl group in these compounds is more mobile and may be readily replaced with the amino group by heating with ammonia. Ether and ester formation takes place more readily with naphthols than with phenols.³⁰ A hydroxyl group attached to the hydrogenated ring of hydronaphthalenes behaves as the hydroxyl group in an aliphatic alcohol.

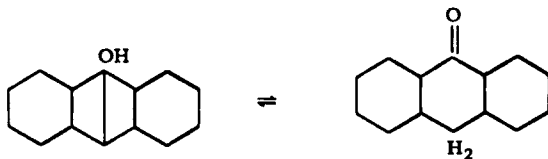
Tautomerism in Phenolic Compounds

Meta di- and trihydric phenols are capable of reacting in the tautomeric keto form. This is particularly true of phloroglucinol which yields a trioxime derived from the keto form:



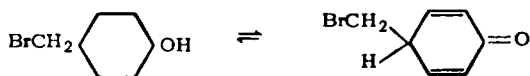
The trioxime is explosible. Tetra-, penta-, and hexaalkylated derivatives of the keto form are obtained when phloroglucinol is heated with alkyl iodides in the presence of alcoholic alkali. Alkylated ketones are also obtained by this treatment from resorcinol. The ease of conversion of phloroglucinol to cyclohexanetriol³¹ and of resorcinol to dihydroresorcinol³² by reduction with sodium amalgam is probably due to the tendency of these phenols to tautomerize to the keto form.

A similar tautomerism is observed in γ -hydroxyanthracenes, which are converted to anthrones by boiling glacial acetic acid



The same type of transformation has been noted also with anthrahydroquinone.³³

A keto-enol isomerism is also shown by *ortho*- and *para*-halomethylphenols:



The quinoid forms of these compounds are termed "pseudophenols." These bodies are converted to methylene quinones when treated with sodium acetate or dilute alkalis. The *ortho*-methylene quinones are formed more readily than the *para* compounds, the

latter readily passing into condensation products and polymers. *Para*-methylenequinones are highly reactive and combine with water, alcohols and acids, forming hydroxy derivatives, their ethers or esters. *Ortho*-methylenequinones are relatively unreactive.³⁴

PHENOL ETHERS

Methods of Formation

The direct conversion of phenols to alkyl ethers by reaction with alcohols in the liquid phase at atmospheric pressure is not possible except in a few isolated cases. Hydroresorcinols,³⁵ for example, and phloroglucinol³⁶ may be etherified by reaction with alcohols in the presence of hydrochloric acid; naphthols,³⁷ α - and β -anthranols, phenanthranol and dihydroxyanthracenes may also be etherified by this method.³⁸ Good yields of ethers are obtained with 3-bromo-2-naphthol by this method, but yields are poor with 1-bromo-, 1-chloro-, 1,3-dibromo-, and 1-chloro-3-bromo-2-naphthols, and no ether formation is observed with 1,3-dichloro-, 1-nitro-, 1-nitro-3-chloro- and 1,3,4-trichloro-2-naphthol.³⁹ Ether formation takes place directly from phenols and alcohols on conducting a mixture of the vapors of the phenol and alcohol over thoria heated to 420°.⁴⁰

Phenol ethers may be readily obtained through the reaction of alkali phenolates with alkyl halides:⁴¹

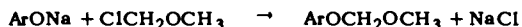


This is the basis of the well-known *Williamson Reaction*. A convenient modification of the method is to dissolve the phenol in an equal weight of acetone and to heat the solution with the required quantity of alkyl iodide in the presence of potassium carbonate.⁴² Allyl ethers may be obtained in yields ranging from 86 to 97% by this modification, although the method does not work satisfactorily with weakly acidic phenols and phenolic aldehydes, the latter giving condensation products in the presence of potassium carbonate.

The solvent has an important influence on the course of the reaction with certain halides. Allyl bromide, cinnamyl bromide and benzyl halides reacting with sodium phenolates in non-dissociating solvents, such as benzene or toluene, give nuclear substituted phenols, whereas in methyl alcohol and in similar solvents the ether is formed.⁴³ The proportion of alkylated phenols formed with allyl bromide and phenol is 70%, cinnamyl bromide and cresol, 60%, α , γ -dimethallyl bromide and cresol, quantitative. Substituted derivatives are formed also from α - and β -naphthols.

Nuclear substitutions, under different conditions, have also been observed with dihydric phenols, particularly when the hydroxyl groups are *meta* to one another.⁴⁴

Sodium phenolates react with chloromethyl ether to form the methoxy methyl ethers of the phenols:



This offers an excellent method of protection of phenolic hydroxyl groups in reactions carried out in alkaline media.

Aryl halides are comparatively unreactive, and the formation of purely aromatic ethers through the interaction of aryl halides with alkali phenolates does

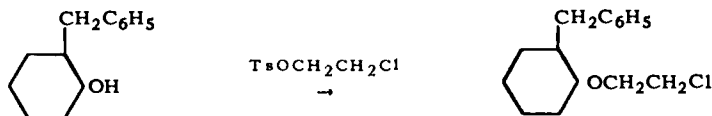
not proceed readily. The reaction between bromobenzene and sodium phenolates, for example requires heating to about 300°. The addition of a little copper bronze accelerates the reaction. Nitro halo benzenes react more readily than unsubstituted aryl halides. Nitro halides in which the nitro group is in *ortho* or *para* position react with sodium phenolates without the use of copper bronze.

Phenol ethers may be prepared also by the reaction of alkali phenolates with dialkyl sulfates or *p*-toluenesulfonic esters.⁴⁵ The general procedure is to shake the phenol in aqueous alkaline solution with slightly more than the required amount of dimethyl sulfate. Alkylation by this method does not proceed readily in some instances as, for example, with *o*-nitrophenols and polyhydroxy-anthraquinones. In such cases the dry salt of the phenol is heated with dimethyl sulfate to between 110 and 160°.⁴⁶

*Freudenberg's method*¹⁹⁶ involves the simultaneous hydrolysis of a phenol acetate and methylation of the resulting phenol with dimethyl sulfate. The method is particularly suited for the methylation of phloroglucinol, which gives poor yields of the ether by other methods. The procedure is to dissolve the phenol acetate, together with an excess of dimethyl sulfate, in boiling methanol, and to add concentrated sodium hydroxide solution with good agitation. A complex of the phenol acetate with dimethyl sulfate is apparently formed first and breaks down to the methylphenolate, sodium acetate and sodium methyl sulfate. It is important to use a large excess of dimethyl sulfate and to keep the water content of the reaction mixture low.

Phenol ethers are formed through the reaction of aromatic diazonium compounds with alcohols.⁴⁷ Hydrocarbons are also formed, however, in this reaction. Purely aromatic ethers may also be prepared by this method; diphenyl ether results, for example, on shaking an aqueous solution of diazobenzene chloride with phenol and gently warming the mixture.

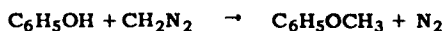
The β -chloroethyl ether of *o*-benzylphenol has been obtained in 89% yield by refluxing the phenol for 16 hours with a solution of β -chloroethyl-*p*-toluenesulfonate in the presence of sodium amide under an atmosphere of nitrogen:²⁷⁷



The toluenesulfonyl esters of dinitrophenols form quaternary salts with pyridine; on treating these with phenols, they are converted to diphenyl ethers in good yield.⁴⁸ The quaternary compound may be prepared by treating a solution of the dinitrophenol in hot pyridine with toluenesulfonyl chloride. The ethers are obtained on adding the appropriate phenol to the solution of the resulting quaternary compound. The reaction may also be carried out in liquid ammonia, sulfur dioxide, or in an excess of the phenol acting as a solvent. The reaction is of fairly general scope and is applicable to aromatic compounds containing an amido group in the side chain, including derivatives of tyrosine.

The methyl ether of phenol is formed, with elimination of carbon dioxide, when methyl phenyl carbonate is heated.⁴⁹

Phenols may be converted to their methyl ethers by reaction with diazomethane:⁵⁰



Purely aromatic ethers may be prepared from phenols through elimination of water with aluminum chloride or zinc chloride, although the reaction does not proceed readily.⁵¹

Olefins combine with phenols in the presence of sulfuric or phosphoric acid to form phenyl alkyl ethers; but the ethers undergo partial rearrangement to alkyl phenols.⁵²

Nitrophenols in which the nitro groups are in the *ortho* or *para* position give the normal stable colorless ethers and, in addition, colored quinoid compounds, such as $\text{O} = \text{C}_6\text{H}_4 = \text{NOOCH}_3$. *Meta*-nitrophenols only yield the stable colorless ether.

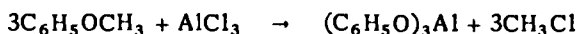
Behavior and Reactions of Phenol Ethers

Fission of Phenol Ethers

Phenol ethers are generally unaffected by alkalis, but they are decomposed on prolonged heating with alcoholic potassium hydroxide at high temperatures.⁵³ Ethers of polyhydric phenols may also be decomposed by this treatment, veratrol giving, for example, guaiacol. Negative substituents, NO_2 , COOH , etc., in the nucleus of aryl alkyl ethers render these compounds susceptible to hydrolysis by alkalis. Thus, *ortho* and *para* nitroanisoles are slowly hydrolyzed when heated with aqueous alcoholic sodium hydroxide under atmospheric pressure. The decomposition of di- and trinitroanisoles is effected with greater ease. Diphenyl ethers with nitro groups in *ortho* and *para* positions are cleaved by treatment with piperidine.⁵⁴

Aryl alkyl ethers may be decomposed by heating with concentrated hydrochloric or hydrobromic acid in a sealed tube at 130 to 140°; they may also be decomposed by refluxing with a mixture of concentrated hydrobromic and acetic acids.⁵⁵ Zeisel's method of determination of methoxy groups makes use of the decomposition of phenolic methyl ethers with hot concentrated hydriodic acid, with the formation of methyl iodide.⁵⁶ Unsubstituted diaryl ethers are comparatively resistant to the action of concentrated hydriodic acid; diphenyl ether is apparently attacked by this reagent at about 250°. Treatment of aryl alkyl ethers with nitric or sulfuric acids leads to the formation of nitrated or sulfonated ethers.

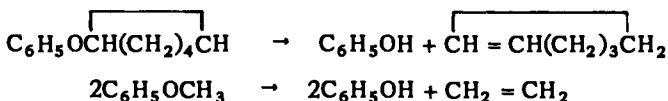
Phenol ethers are readily decomposed by aluminum chloride or bromide:⁵⁷



Homologs of phenol are also formed in small amount in this reaction. Aniline hydrochloride also causes the fission of phenol ethers.⁵⁸ Dealkylation may be brought about by heating with pyridine hydrochloride.³⁰⁰

Certain aryl alkyl ethers are decomposed by sodium at high temperatures.³⁰¹ β -Naphthyl ethyl ether heated at 140° with this metal yields sodium β -naphtholate and sodium ethoxide, together with some naphthalene and ethylene. Phenetole is decomposed at 200–260°. Unsubstituted diaryl ethers are comparatively stable to concentrated hydriodic acid; diphenyl ether is apparently attacked however at 250°.

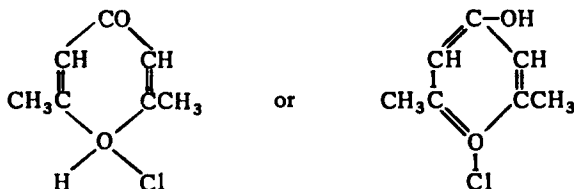
Aliphatic and cycloaliphatic phenol ethers decompose to phenol and unsaturated hydrocarbons when heated somewhat below 400°:



Decomposition takes place more readily if an ethylenic bond is present in the aliphatic group, as in $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_3$.

Oxonium Compounds

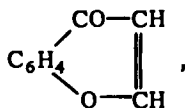
Phenol ethers combine with acids to form the so-called oxonium compounds.⁵⁹ This property is shared by many other types of oxygen compounds, but the tendency to form oxonium compounds is very marked in ethers, especially ethers of cyclic structure. Typical of such cyclic ethers is 2,6-dimethyl- γ -pyrone, the hydrochloride of which has the structure⁶⁰



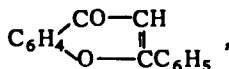
It is of interest to note that these ethers are also capable of forming coordination compounds with certain metallic salts.

Many oxonium salts are crystalline compounds soluble in water; the phosphomolybdate is almost insoluble in water. Free dimethyl- γ -pyrone is basic in reaction and of about the same strength as urea,⁶¹ although it reacts as a weak acid toward strong bases;⁶² it forms an addition compound with methyl iodide.⁶³ Pyrone itself is a distinctly basic body, though weaker than dimethyl- and tetramethylpyrone.⁶⁴

Chromone,

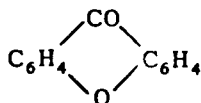


gives a fairly stable hydrochloride.⁶⁵ Flavone,



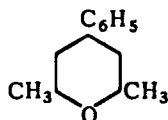
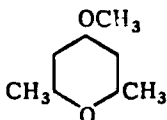
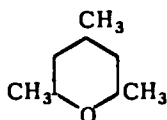
gives salts which are less stable than those of pyrone and are completely decomposed with water. On the other hand, the natural yellow coloring matters derived from this substance form more stable salts. Thus, crystalline salts have been prepared from myricetin, quercetin, rhamnetin, rhamnazin, morin, luteolin and fisetin. The hydrochlorides, bromides and iodides of all these compounds, except those of rhamnetin and rhamnazin have also been made.⁶⁶

Hydrochlorides have been prepared from xanthone,



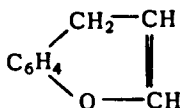
and various hydroxyxanthenes such as euxanthone, gentisein, datiscetin, etc.⁶⁷ β -Phenonaphthoxanthone and methoxyxanthone give yellow hydrobromides.⁶⁸

The ability to form salts with acids is shown to a marked degree by many derivatives of γ -pyran; these are known as *pyrylium* or *pyroxonium* compounds. Among the simpler compounds of this class are derivatives of 2,6-dimethylpyran⁶⁹ such as the following:

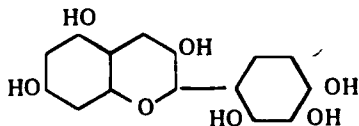
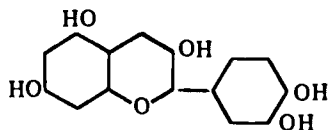
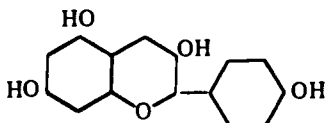


Substitution of the meso hydrogen by a phenyl group increases the stability of carboxonium salts.

Benzopyrylium

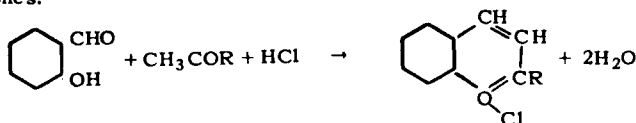


forms oxonium salts. The red, violet and blue coloring matters in blossoms and berries, the so-called anthocyanines, are glucosides of bodies derived from trihydroxybenzopyran, namely pelargonidin, cyanidin and delphinidin,⁷⁰ the formulas of which are presented below:

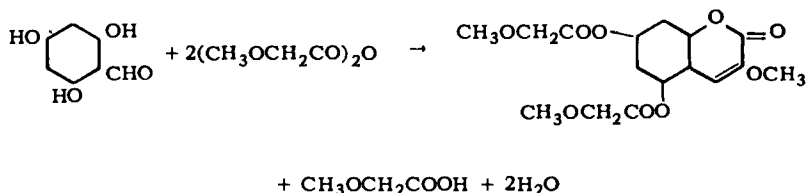


These substances all give oxonium salts.

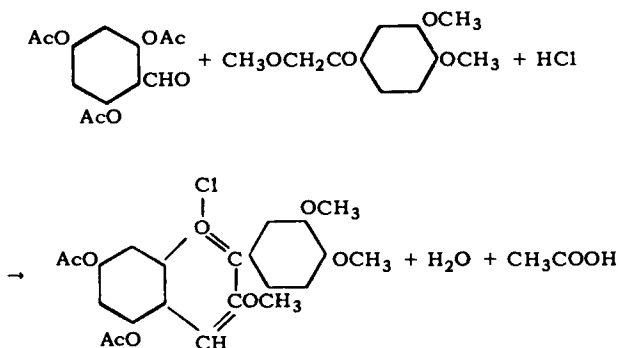
Benzopyrylium derivatives have been synthesized through the condensation of aromatic phenol aldehydes with esters or ketones under the influence of hydrochloric acid.⁷¹ Benzopyrylium derivatives have been obtained through the condensation of salicylaldehyde and ketones:



and from phloroglucinolaldehyde and methoxy acetic anhydride⁷²



Pelargonin and other similar compounds have been synthesized from this condensation product. Similar products have been prepared by the condensation of triacetylphloroglucinolaldehyde with acetophenone derivatives:⁷³



The use of the acetylated phloroglucinolaldehyde in such reactions is desirable, since the free aldehyde undergoes self-condensation very readily. Protection may be achieved also by methylating the hydroxyl groups in phloroglucinol aldehyde. The condensation is best carried out in ethyl acetate solution. The hydrolysis of the crude product is brought about by treatment with cold aqueous sodium hydroxide in an indifferent atmosphere.

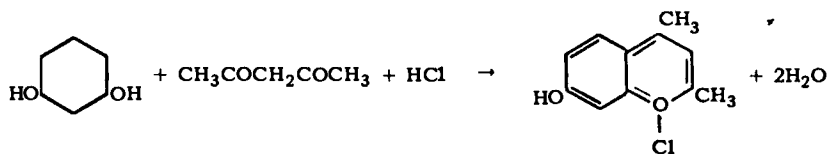
The reaction is of very wide applicability, even though the simpler flavinium salts cannot be prepared by this method.

In the preparation of 2-methylbenzopyrylium salts, appreciable amounts of a 2-vinyl derivative may be formed as a result of the condensation of the aldehyde with the reactive 5-methyl group in the pyrylium compound. The vinyl derivative usually undergoes rearrangement to a spiropyran which, occasionally, may be the only product of the reaction.

In the condensation of unsymmetrical ketones of the type $\text{CH}_3\text{COCH}_2\text{R}$ both the methyl and methylene group are capable of entering the reaction and the direction in which the condensation proceeds depends on whether it is carried out in alkaline or acid solution. Condensation with the methylene group is favored in acid solution, and with the methyl group in alkaline medium. Exceptions to this generalization exist however.

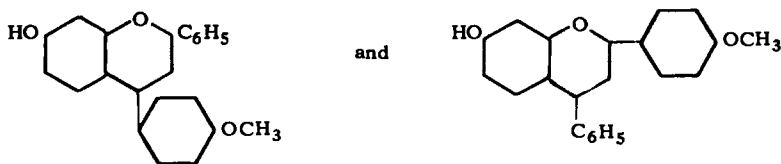
It is often of advantage to prepare the intermediate chalcone in the pure form. Cyclization of the chalcone to the pyrylium compound proceeds in an unambiguous manner. This procedure has the further advantage that it offers a greater latitude in the choice of solvent used as the reaction medium. *o*-Hydroxybenzylidenes often accompany the chalcones in the reaction. The cyclization of the former gives 4-phenylflavylium salts which may contaminate the final product.

Benzopyrylium derivatives have also been obtained through the condensation of diketones with phenols:⁷⁴



A great number of compounds of this type have been prepared by this method. The procedure followed was to dissolve the components in acetic acid and to conduct a current of hydrogen chloride through the solution, whereupon the chloride of the oxonium compound separated in the crystalline form. Methylation of the hydroxyl groups, which can be brought about by use of methyl sulfate, stabilizes the bases considerably.⁷⁵

Isomeric compounds may form in this reaction. Thus, in the reaction of resorcinol with benzoylanisoylmethane, a mixture of the compounds



is formed.

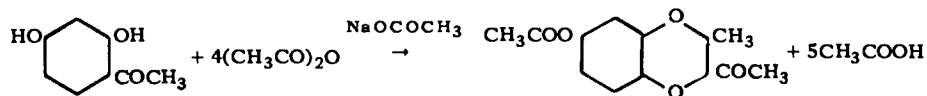
An extension of this synthesis is the condensation of an o-hydroxybenzaldehyde with a reactive phenol under the influence of hydrogen chloride to a xanthylum salt.

The condensation of phenols with β -keto esters under the action of phosphoric oxide has been employed extensively for the synthesis of chromones (*Simonis reaction*).²²⁰ Chromones may be obtained by this method from simple monohydric phenols and quinol, but resorcinol, orcinol, pyrogallol, phloroglucinol and α -naphthol give coumarins.

As an example, the preparation of 1,2-dimethylchromone from phenol and methyl acetoacetate may be mentioned: To a solution of 50 gm dry phenol and an equal weight of methyl acetoacetate are added 75 gm phosphorus pentoxide, the mixture is well agitated for 15 minutes with external cooling, and is then heated at 100° for two hours. Additional 50 gm quantities of phenol and phosphorus pentoxide are added, the mixture being heated for two hours, and this is repeated once more. The addition of some absolute alcohol to prevent caking is essential for the success of the reaction.

A modification of the method utilizes the sodio compound of the keto ester instead of the keto ester, when direct reaction between the phenol and keto ester fails to proceed, apparently because the phenol prevents the enolization of the keto ester.

Hydroxyacetophenones with a hydroxyl group in position 2 give chromones when treated with a mixture of the anhydride and the sodium salt of an acid (*Koatsnecki's reaction*):²²¹

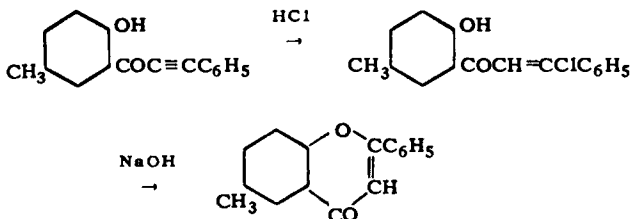


Hydrolysis of the acyloxy compound formed gives the free chromone. The reaction has been applied successfully to o-hydroxy ketones $\text{HOC}_6\text{H}_4\text{COCH}_2\text{R}$ in which R is H, a normal alkyl group with up to 16 carbon atoms, or a phenyl, substituted phenyl, benzyl, alkoxy and acyloxy group, or a halogen. The reaction has been employed for the preparation of naphthopyrones from acetylnaphthols.²²² Satisfactory results have been obtained with anhydrides $(\text{R}'\text{CO})_2\text{O}$, in which R' is an isopropyl, chloromethyl, phenyl, substituted phenyl, phenethyl or styryl group.

Coumarin formation often accompanies the principal reaction with anhydrides bearing more than one α -hydrogen. Phenylacetic anhydride gives coumarins almost exclusively, and coumarins are the principal product in some of the reactions with acetic and propionic anhydrides.

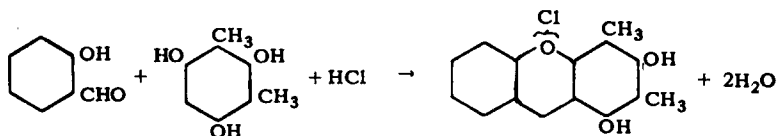
o-Hydroxypropiofenones show a greater tendency to form chromones than *o*-hydroxyacetophenones, but *o*-hydroxyisobutyrophenones give only coumarins.²⁹⁰

The acetylenic ketone obtained through the condensation of phenylpropiolyl chloride, $\text{C}_6\text{H}_5\text{C}\equiv\text{CCOCl}$, with *p*-cresol methyl ether adds the elements of hydrogen chloride in the presence of aluminum chloride. The resulting compound may be cyclized with dilute sodium hydroxide to a 6-methylflavone:²⁷⁸



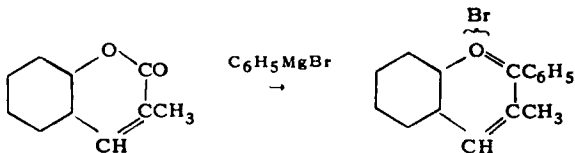
Other flavones have been synthesized by this method.

Xanthylium salts have been prepared through the condensation of *o*-hydroxy aromatic aldehydes with reactive phenols in the presence of hydrogen chloride:²²³



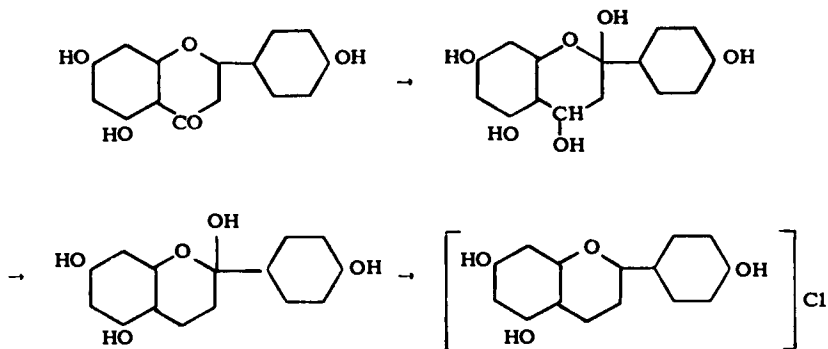
Bülow's very generally applicable method, which is a variant of this, involves the reaction of a phenol with a keto aldehyde.²²⁴

Coumarins substituted in the 3-position can be converted readily to 2-phenylbenzopyrylium salts by treatment in dilute solution and at room temperature with phenylmagnesium bromide:²²⁵



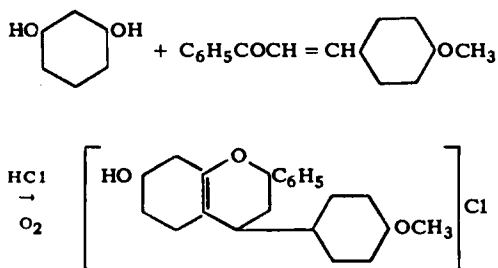
2,4-Diphenyl- Δ^2 -chromenes are formed, however, when the reaction is carried out in hot, concentrated solution.¹⁹⁰ Chromenes of this type are also formed under these vigorous conditions from 4-substituted coumarins, but benzopyrylium salts are obtained in poor yield from such coumarins under milder reaction conditions. The reaction has been extended to the preparation of 4-substituted benzopyrylium salts from chromones.

Flavylium chlorides have been obtained through the reduction of flavones and flavonones in an alkaline medium.²²⁶ Reduction is effected by suspending the compound in water and treating with sodium amalgam. Addition of a hydrogen halide after removal of the free mercury gives the flavylium halide. The reduction of apigenin is believed to proceed in the stages shown below:



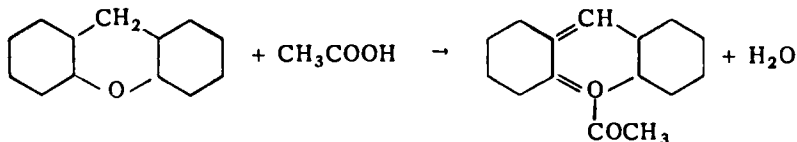
Magnesium and hydrochloric acid have also been used as the reducing agent. Quercetin remains unaffected under the conditions of this reaction.

The reaction of an unsaturated aldehyde or ketone with a reactive phenol in the presence of an *oxidizing agent* has also been utilized for the synthesis of pyrylium compounds.²²⁷ 7-Hydroxy-4-anisylflavylium chloride has been obtained by this method from resorcinol and anisylideneacetophenone:

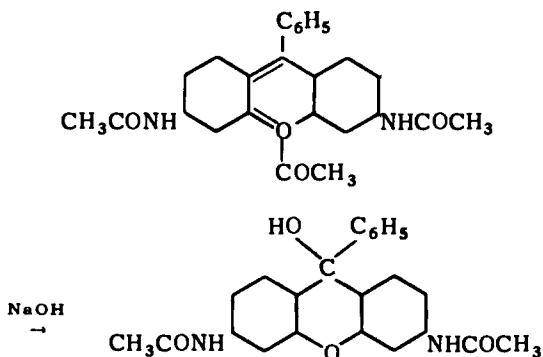


Chloranil was employed as the oxidizing agent in this reaction. Bromine has also been used successfully for the purpose.

Xanthanol itself gives yellow salts with acids:

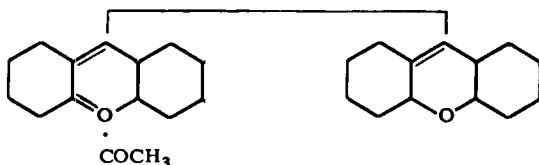


Some of the more remarkable carboxonium salts have been prepared from certain derivatives of xanthone. The esters of dimethoxyphenylxanthylumcarboxylic acid form salts which are hardly decomposed by water, and are of neutral reaction. When the solution of the chloride is shaken with freshly precipitated silver oxide, a solution of the free base is obtained which reacts alkaline.⁷⁶ Other derivatives of this type of still greater stability are known.⁷⁷ Diaceta-minophenylxanthylum salts, which show great similarities with phenylxanthylum salts, are partially decomposed with water and are converted to the pseudo base by weak alkalies:



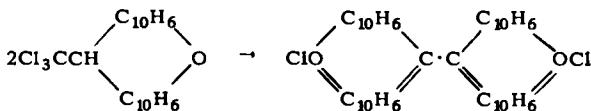
Phenyldinaphthoxanthylum gives very stable salts.

When xanthone is reduced in acetic acid solution with hydrogen bromide and zinc dust, the zinc bromide complex of the dioxanthylum salt:

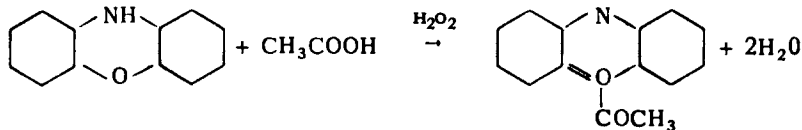


is obtained.

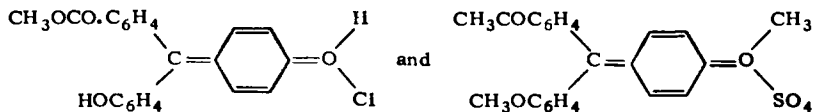
Chloral- β -dinaphthalene oxide gives on oxidation with manganese dioxide and hydrogen chloride in acetic acid a similar dioxanthylum salt:



Oxonium salts have been obtained also from *oxazines*; phenoxazine, for example, yields an acetate by reaction with acetic acid in the presence of an oxidizing agent, such as hydrogen peroxide:

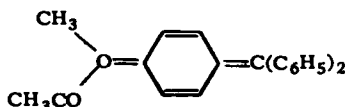


Oxonium salts may be prepared from the methyl ester of phenolphthalein and its dimethyl ether, such as the following:⁷⁸



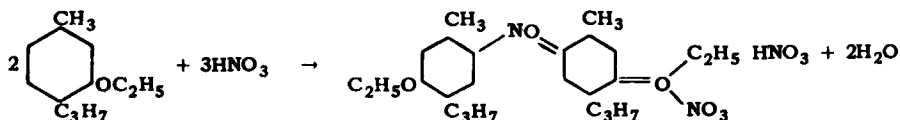
Oxonium salts also have been made from hydroxy derivatives of triphenylcarbinol and

related compounds. These compounds also give *p*-quinoid salts; thus, *p*-anisyl-diphenylcarbinol yields the salt



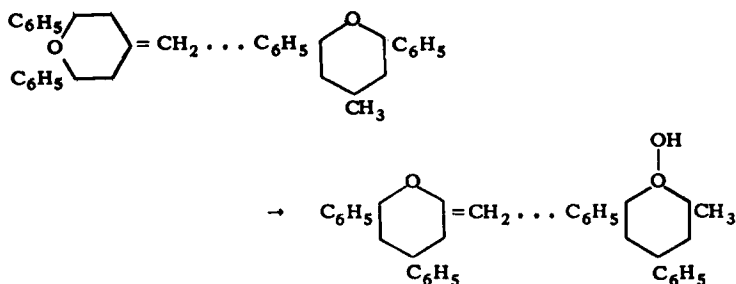
Similar compounds have been obtained from other triphenylcarbinol ethers. Those methoxyphenylcarbinols in which one or more methoxy groups are present in the *para* position with respect to the central carbon atom, give the most stable salts. Methoxy groups in the *ortho* position also exert a stabilizing effect, but those in the *meta* position are practically without influence.

Many simple phenol ethers yield oxonium salts; when nitric acid is employed in the reaction, nitration and coupling of two molecules may occur. Thus, with thymol ethyl ether the following reaction takes place:⁷⁹



The methyl, isopropyl, *n*-butyl and benzyl ethers of thymol also give similar compounds. Substances of the same type have been prepared from paraxyleneol. A perchlorate of the same type has been prepared from anisol, and from resorcinol dimethyl ether.

Pyrylium compounds, which have at least one methyl group in the 2 or 3 position, are capable of forming phenopyrylium compounds through the intermolecular combination of two molecules of the compound. As examples may be cited the intermolecular compounds of 4-methyl-2,6-diphenylpyrylium and of 2-methyl-4,-6-diphenylpyrylium:⁸⁰



In addition to true oxonium compounds, there are also known compounds in which the four valencies of oxygen are satisfied with carbon bonds; these have the character of loose combinations.

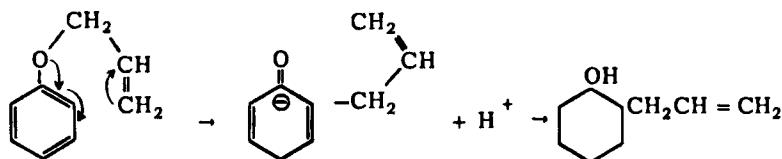
Claisen's Rearrangement⁸¹

Allyl ethers of phenols undergo rearrangement to allyl phenols when heated, the allyl group entering the *ortho* position if this is available. The transformation is rather general in character and was observed first in aliphatic com-

pounds.⁸² The condition of rearrangement is that the grouping $\text{—}\overset{\text{C}}{\text{=}}\overset{\text{C}}{\text{—}}\overset{\text{C}}{\text{—}}\text{O—}\overset{\text{C}}{\text{=}}\overset{\text{C}}{\text{—}}$

be present in the molecule. In this sequence the ethylenic linkage to the right of the oxygen atom may be present within an aliphatic group, or in an aromatic nucleus.

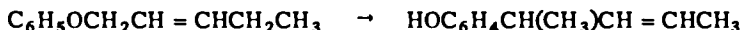
Attachment of the allyl group to the *ortho* position proceeds *intramolecularly*, probably in accordance with a scheme such as the following:⁸³



It is evident that if the transformation takes place by this mechanism, then the allyl group is *inverted*, the γ -carbon atom in the group becoming attached to the *ortho* carbon atom in the benzene nucleus. There is ample experimental evidence that inversion actually takes place. It has been demonstrated, for example, that crotyl phenyl ether, $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}=\text{CHCH}_3$, rearranges to the branched chain *o*-methallylphenol, $\text{HOC}_6\text{H}_4\text{CH}(\text{CH}_3)\text{CH}=\text{CH}_2$.

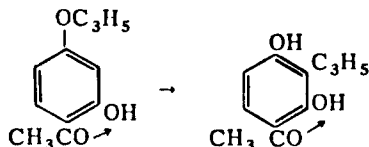
If both *ortho* positions in the benzene nucleus are occupied by substituents, then the allyl group migrates to the *para* position, though never to the *meta* position,⁸⁴ even when a substituent is present in the *para* position. Migration to the *para* position apparently takes place *intermolecularly* and is not accompanied by inversion⁸⁵ except in one known instance, namely in the rearrangement of α -ethylallyl 2-carbomethoxy-6-methylphenyl ether.⁸⁶ A few compounds are known in which the allyl group migrates to the *para* position even though an *ortho* position is available; it is probably of significance that all these compounds are derivatives of polyhydroxybenzenes.⁸⁷

In the rearrangement of γ -ethylallyl phenyl ether, the unsaturated group becomes attached to the *ortho* carbon atom in the nucleus by the δ -carbon atom:⁸⁸



In the γ -propylallyl series, the C atom in the ϵ position becomes attached to the nuclear carbon atom. α -Substituted allyl ethers give the normal inversion product.

The monoallyl ether of resacetophenone rearranges with the migration of the allyl group to the 3-position because of the fixation of the double bond at the 3,4-position due to chelation:⁸⁹



With the monoallyl methyl ether, which is incapable of chelation, the allyl group migrates to the 5-position.

In the polycyclic series, where the position of the double bonds is fixed, migration may become impossible because of the presence of a substituent in

the position where the allyl group would become normally attached.⁹⁰ Thus, 1-allyl-2-allyloxynaphthalene and 1,5-diallyl-2,6-diallyloxynaphthalene do not undergo the allylic rearrangement.

The allylic rearrangement is strictly confined to allyl ethers; phenyl Δ^3 -butenyl ether and phenyl vinyl ether, for example, do not undergo the rearrangement.⁹¹ Acetylenic compounds of the type of $C_6H_5OCH_2C\equiv CH$ also fail to undergo the rearrangement.

The allylic rearrangement has been observed also among heterocyclic compounds; the rearrangement has been carried out with allyl ethers of fluorescein, quinaldine, flavone, chromone, dibenzofuran and coumarin.

Allyl ethers of *thiophenols* also undergo the Claisen rearrangement, although less readily than the phenolic ethers. Allyl *p*-tolyl sulfide, for example, gives 2-allyl-4-methylthiophenol in 27% yield on 4 hours' heating at 228-264°.⁹²

The procedure in carrying out the Claisen rearrangement is to reflux the ether for a sufficient period; conversion is complete when the boiling point of the liquid no longer rises. If the ether boils much above 200°, refluxing may be carried out under vacuum, or a lower boiling solvent may be added to decrease the refluxing temperature. The transformation is exothermic and it may be necessary to proceed with caution when working with larger quantities. The solvents most commonly employed are dimethyl and diethylaniline. Paraffin oil, tetralin and kerosene have also been employed with satisfactory results. It is desirable to maintain a non-oxidizing atmosphere over the ether during refluxing.

Experience with a variety of allyl ethers has indicated that in general it is not necessary to heat them above 200° to effect rearrangement, and that many of the transformations proceed readily at a much lower temperature.

Allylation of phenols by the Claisen rearrangement may be repeated, but a maximum of only three allyl groups may be introduced into the benzene nucleus by this method.

The allylic rearrangement is usually accompanied by the formation of a phenol and a diene in small quantities. The formation of phenol and diene is favored by increased substitution in the allyl group.⁹³ The highly substituted $\alpha,\alpha,\gamma,\gamma$ -tetramethylallyl phenyl ether undergoes only the cleavage reaction without rearrangement. Another side reaction encountered during the allylic rearrangement of certain phenols is the formation of a dihydrobenzofuran. Compounds with substituted allyl groups seem to give rise to dihydrobenzofurans more readily than unsubstituted allyl compounds.

Allyl aryl ethers with halogen atoms in the allyl group do not readily undergo the allylic rearrangement;⁹⁴ the γ -halo ethers such as $C_6H_5OCH_2CH = CHCl$ do not undergo the rearrangement at all. Substituents in the aromatic nucleus do not greatly affect the ease of rearrangement. Rearrangement to the *para* position proceeds poorly when two allyl groups or bromine atoms are present in the *ortho* positions.

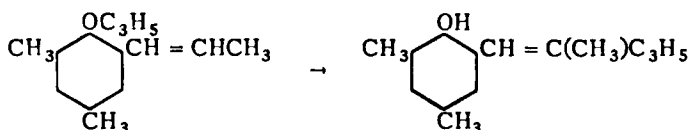
Free carboxyl groups and aldehyde groups in *ortho* or *para* position may be removed and replaced by allylic groups in the course of allylic rearrangement;⁹⁵ ester groups at these positions are not thus removed. Partial replacement of chlorine has been observed in the rearrangement of allyl-2,6-dichlorophenyl ether, resulting in the formation of about 10% of 2-allyl-6-chlorophenol, along with 60% of the expected normal rearrangement product.⁹⁶ A similar behavior is shown by allyl 2,6-dibromophenyl ether.

Allyl phenols undergo isomerization to propenyl compounds under the influence of hot alcoholic potassium hydroxide, powdered solid alkalies, potassium phenolate, etc.

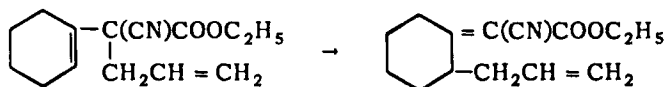
The furyl group possesses the necessary structure for the allylic rearrangement, and it has been possible to prepare *o*-furfurylphenol in 78% yield from furyl phenyl ether.²⁷⁹

Other Allylic Rearrangements

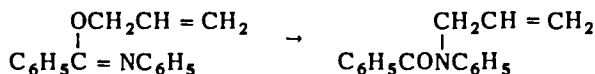
Allyl ethers of the type of allyl 1-propenyl-4,6-dimethylphenolate can be rearranged to phenols with the allyl group attached to the side chain:⁹⁷



The allyl group in ethyl 1-cyclohexenylallylcynoacetate migrates into the ring to form ethyl (2-allylcyclohexylidene)cynoacetate when the compound is heated 10 hours at 170°:⁹⁸



The allyl group in allyl N-phenylbenzimidazole ether migrates to the nitrogen atom on heating 3 hours at 210–215°:⁹⁹



2-Allyloxyquinoline rearranges to N-allyl-2-quinolone on distillation at 325°.¹⁰⁰ A similar migration from oxygen to nitrogen takes place with 2,6-allyloxy-7-methylpurine.¹⁰¹

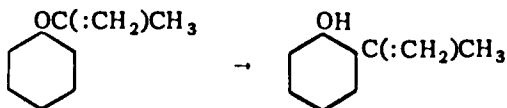
Rearrangement of other Phenol Ethers

Several cases are on record in which a tertiary and secondary alkyl group or a benzyl group migrates from oxygen to the nucleus under the action of heat. The rearrangement is intermolecular and the migrating group may enter the *ortho* or the *para* position. Tertiary alkyl groups migrate rather readily, while normal saturated alkyl groups do not migrate at all. The rearrangement of the isopropenyl ether gives mainly the *ortho* derivative,¹⁰² and isobutyl, *sec*-butyl and *tert*-butyl phenyl ethers all give the same *p*-*tert*-butylphenol when the rearrangement is carried out in the presence of aluminum chloride, the migrating group undergoing isomerization during the rearrangement of the iso and *sec*-butyl ethers.¹⁰³ Phenyl *tert*-butyl ether gives *p*-*tert*-butylphenol; benzyl phenyl, benzyl *p*-tolyl and benzyl guaiacyl ethers yield the corresponding *p*-benzyl and dibenzyl derivatives, in addition to phenol, *o*-cresol and guaiacol respectively.

Benzyl α - and β -naphthyl ethers give 4-benzyl- α -naphthol and 1-benzyl- β -naphthol respectively, together with the naphthols themselves.

*The Niederl-Storch Reaction*¹⁰²

Isopropenyl phenyl ethers undergo molecular rearrangement when heated with a solution of 10% acetic acid in sulfuric acid for a long period, giving an unsaturated phenol:



The unsaturated phenol is also obtained when phenol is treated at 0° with a mixture of propyl alcohol and 1/5 molecular equivalent of sulfuric acid, and the product is distilled. The alkyl group enters the *ortho* position, unless both *ortho* positions are already occupied, in which case the group enters the *para* position.

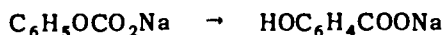
PHENOL ESTERS

Phenolic esters of organic acids may be readily obtained by gently warming a mixture in molecular proportions of the acid anhydride and phenol and gradually adding 1/3 molecular proportion of phosphorus oxychloride.¹⁰⁴ In many instances acetylation of the phenolic hydroxyl group may be accomplished through the action of acetic anhydride in the presence of anhydrous sodium acetate.¹⁰⁵ This is known as the *Liebermann-Hörmann method*. The propionic ester of phenol has been prepared by heating a mixture of phenol and propionyl chloride until the evolution of hydrogen chloride ceased. All the hydroxyl groups in a polyhydric phenol may be acetylated by treating a solution of the phenol in dilute aqueous alkalis with acetic anhydride.¹⁰⁶

Carbonic esters of phenols are formed very readily when a current of dry carbon dioxide is conducted over dry powdered alkali phenolates:¹⁰⁷



These compounds are converted on heating to the alkali metal salts of phenolic acids:



The neutral phosphoric esters of phenols can be obtained through the reaction of the alkali metal salts of the phenol with phosphorus oxychloride, or by heating a mixture of the phenol and phosphorus oxychloride with a tertiary base under reflux for a prolonged period. When heated with potassium cyanide, these esters give the corresponding nitrile.¹⁰⁸ Sulfuric esters may also be prepared similarly. Alkylated sulfuric and phosphoric esters are readily converted by alkaline permanganate to phenol carboxylic acid derivatives,¹⁰⁹ while

the free phenols undergo deep-seated decomposition on treatment with permanganate.

Sulfur dioxide is adsorbed by dry alkali phenolates, which are thereby converted to phenol sulfates; these, on heating, undergo molecular rearrangement, forming phenolsulfonic acids.

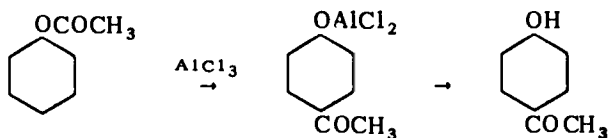
Phenol sulfuric esters are obtained in the form of their potassium salt on gently heating a concentrated solution of the potassium salt of the phenol with potassium pyrosulfate:¹¹⁰



Phenol esters are readily decomposed to their component phenol and acid when boiled with alkalis, or even with water alone.

Fries Reaction¹¹¹

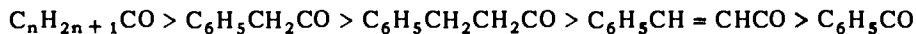
An organic ester of a phenol heated with aluminum chloride is converted to a *para* or *ortho* hydroxy ketone:



This rearrangement possesses preparative importance, because the direct introduction of acyl groups into phenols by the Friedel-Crafts reaction does not proceed readily. The rearrangement takes place rapidly at 180-200° in a melt of aluminum chloride and sodium chloride. An important application of the reaction is the preparation of 4-chloroacetylpyrocatechol, an intermediate in the synthesis of adrenaline.¹¹²

The *para* isomer is formed at low temperatures, while the formation of the *ortho* acylated compound requires heating to a high temperature. For example, the *para*-hydroxy ketone results in 80% yield from *meta*-cresyl acetate when the reaction is carried out at 25°, while at 165° only the *ortho* compound is formed.¹¹³ The *meta* isomer has never been observed to form.

The acyl radical in the phenyl ester may be aliphatic, aromatic, or aryl-aliphatic. The relative ease of rearrangement in increasing order ranges as follows:



No differences have been observed between benzoyl and substituted benzoyl groups. The phenol may be derived from benzene, naphthalene, phenanthrene, biphenyl, or coumarin. An increase in the size of the acyl group favors the formation of the *ortho* compound. *Para* substituted phenol esters furnish only *ortho* hydroxy ketones. A methyl group in the *ortho* position in the phenol ester favors the formation of *p*-hydroxy ketone, while the same group in the *meta* position favors the formation of the *ortho* hydroxy ketones.

The presence of *meta* directing groups, such as nitro, acyl, or carboxyl groups, in the phenol ester causes a decrease in the rate of reaction, or completely prevents the rearrangement. The reaction fails to proceed, for example, if the phenol residue carries a nitro or a benzoyl group in the *ortho* or *para* position; the presence of an acetyl or carboxyl group in the *ortho* position hinders the reaction, while if this group is in the *para* position reaction fails to proceed. Halogens in the nucleus also retard or hinder the rearrangement.

Various mechanisms have been proposed in explanation of the reaction,¹¹⁴ embracing the possibilities of cleavage of the ester to phenolate and acyl chloride, with the subsequent acylation of the phenol; acylation of one molecule of phenol ester by a second molecule of the same; and finally, a true intramolecular rearrangement. No complete proof is available, however, of the correctness of any of these mechanisms.

Procedure

For the preparation of *para* hydroxyketones one molecular proportion of the ester is dissolved in about five times its weight of dry nitrobenzene and 1.2 to 1.3 molecular proportions of aluminum chloride are added in small portions. The mixture is allowed to stand for 24 hours at room temperature, or it may be heated at 60° for half an hour. It is then poured into a mixture of ice and dilute hydrochloric acid, and the resulting solution is heated on the water bath.¹¹⁵ In the case of phenols with long chains, the temperature must be kept below 20° in order to avoid any further rearrangements.

In the preparation of *ortho* hydroxy ketones, one molecular equivalent of the ester is mixed intimately with 1.2 to 1.3 molecular equivalents of aluminum chloride in a flask provided with an air or water condenser. The flask is gradually heated in an oil bath to 120-150°, and the temperature is maintained at this point for 15 minutes.¹¹⁶ After cooling, ice and 10% hydrochloric acid are added to the mixture. In dealing with phenol esters with resistant groups, or when the acyl group must displace an alkyl group present in the nucleus, heating must be continued for half an hour, and occasionally for an hour. Two molecular equivalents of aluminum chloride are required for the rearrangement of esters of dihydric phenols.¹¹⁷

The product may be isolated by taking up with ether and shaking the ethereal solution with 7.5% aqueous potassium hydroxide. The free phenol is subsequently precipitated from the alkaline solution by the addition of 25% hydrochloric acid. The *ortho* and *para* isomers may be separated by distillation with steam, the *ortho* ketone passing over first because of its higher volatility.

Aluminum chloride causes the saponification of alkoxy groups, if such are present in the aromatic nucleus.¹¹⁸

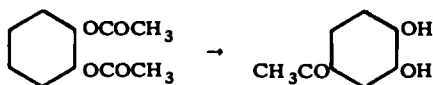
Boron trifluoride has been successfully used for the preparation of the *para* hydroxy ketones at low temperatures.¹¹⁹ Chlorobenzene and tetrachloroethane have been used as solvents in carrying out the reaction at higher temperatures.

The acetyl derivatives are obtained especially readily; thus, thymol acetate is converted to the keto compound quantitatively in 10 minutes at 60°. All aliphatic residues have the same migration velocity; chlor- and bromoacetic esters require a higher temperature. The velocity of rearrangement of esters of phenylacetic, cinnamic and hydrocinnamic acids approaches that of the aliphatic esters.

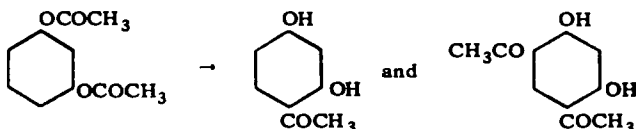
With polyhydric phenols more than one acyl group may be readily introduced into the nucleus by repeated application of the Fries reaction. With phenol,

the entrance of one propionyl group into the *ortho* or *para* position prevents further reaction, although once the propionyl group is reduced to the propyl group, a second alkyl residue may be introduced into the nucleus of the phenol.¹²⁰

Among the esters of *meta*-cresol with aliphatic acids, only the acetate gives a *para*-hydroxy ketone as the principal product; with all the other esters the principal product is the *ortho* hydroxy ketone, even when the reaction is carried out at a low temperature. Catechol diesters yield principally the 4-acyl derivatives and secondarily the 3-isomers:

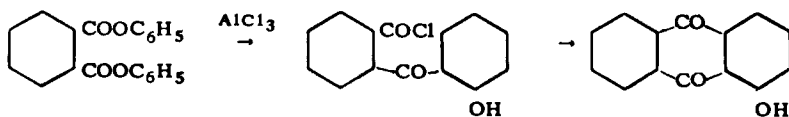


Resorcinol diesters give both mono and diacyl derivatives:



Hydroquinone diacetate fails to undergo the Fries reaction,¹²¹ but the diacetate of 2-methoxy-1,4-dihydroxybenzene, subjected to the reaction, gives 5-acetyl-2-methoxy-1,4-dihydroxybenzene.¹²² With resorcinol esters, 4,6-diacylresorcinols are obtained when the ester in nitrobenzene solution is treated with 2.1 moles of aluminum chloride; on the other hand, 2,6- or 2,4-diacyl derivatives are formed when the esters are heated with 2 moles of aluminum chloride first at 70-130° for half an hour, then at 130° for 3 to 4 hours.¹²³ Acyl derivatives of α -resorcylic acid fail to undergo the rearrangement.¹²² *p*-Cresyl cinnamate suffers decomposition when subjected to the conditions of Fries reaction. 2,6-Dimethoxyphenyl acetate has been reported to yield a *meta* acetyl derivative when treated with zinc chloride at room temperature.¹²⁴

Diphenyl phthalate subjected to the Fries reaction gives 1-hydroxyanthraquinone:¹²⁵



The migration or removal of alkyl groups has been observed with certain di- and trialkyl phenol esters during the Fries rearrangement.¹²⁶ This occurs only with the esters of homologs of *para* xylenols and pseudocuminols. Where there is a tendency toward migration and the *ortho* and *para* positions are occupied, the groups at these positions may be replaced by acyl groups of the ester. Ethyl groups are removed more readily than methyl groups.

In the *biphenyl* series, the entrance of an acyl group into the nucleus of the hydroxyl-free ring has been observed. Aliphatic esters of 2-hydroxybiphenyl give mixtures of 3- and 5-acyl-2-hydroxybiphenyls, the yield of the 3-acyl derivatives increasing with the size of the acyl group.¹²⁷

Esters of α -naphthol subjected to the conditions of Fries reaction at low temperatures give 4-acyl- α -naphthol, while at higher temperatures 2-acyl- and

2,4-diacylnaphthols are formed. β -Naphthyl acetate gives 1-acetyl-2-naphthol, together with a little 6-acetyl-2-naphthol.¹²⁸

Esters of hydroxycoumarin undergo the Fries reaction in normal manner, giving o-hydroxy ketones.¹²⁹ The reaction of esters of 4-methyl-7-hydroxycoumarin provides a route to the synthesis of 2-acyl resorcinols.

The Fries reaction is applicable also to compounds with an acid imino group, such as carbazole. Thus, 3-acetylcarbazole is obtained by heating N-acetylcarbazole with aluminum chloride at 100°. ¹³⁰

Reverse Fries Reaction

Cases are on record in which an acyl group originally in the nucleus of a phenol breaks loose and replaces the hydrogen of the phenolic hydroxyl group to form an ester. The transformation is a reverse Fries Reaction and is observed with p-hydroxyketones having an alkyl group in the ortho position with respect to the acyl group. These compounds are converted to meta-alkyl phenyl esters in excellent yield when heated with sulfuric, camphorsulfonic or phosphoric acid. Thus, 2-methyl-4-hydroxyacetophenone is converted smoothly into meta-cresyl acetate when heated with sulfuric or phosphoric acid.

THIOPHENOLS

Thiophenols may be prepared in good yield through the reduction of aromatic sulfochlorides with aluminum amalgam. The sulfochloride is dissolved in a mixture of alcohol and ether, 150 percent by weight of aluminum amalgam is added and the mixture is boiled one hour, while adding the required quantity of water gradually. The rate of generation of hydrogen is controlled by regulating the rate of addition of water. The volatile thiophenols are isolated by steam distillation.¹³¹ The reduction may be carried out also by use of zinc and sulfuric acid, or with stannous chloride.¹³² Thiophenols may also be prepared through the reduction of aromatic sulfonic acids.

Reduction may be effected also with zinc dust and sulfuric acid. The chloride is added slowly to sixteen times its weight of sulfuric acid maintained at -5 to 0°. Five atomic equivalents of zinc dust are then added as rapidly as possible with good agitation, and without allowing any considerable rise in temperature. Agitation is continued for one to one and a half hours, after which the liquid is slowly heated under reflux and finally boiled until it is clear. The thiophenol formed is recovered by steam distillation.²⁸⁰

The disulfide is obtained when the sulfonyl chloride is dissolved in ten times its weight of alcohol, five atomic equivalents of zinc dust are added, and then hydrochloric acid is introduced. Upon completion of the reaction the liquid is filtered from any unreacted zinc, and any thiophenol present is oxidized to the disulfide by the addition of ferric chloride solution. The disulfide is precipitated out on dilution with water. Yields vary between 50 and 70% of theory.²⁸¹

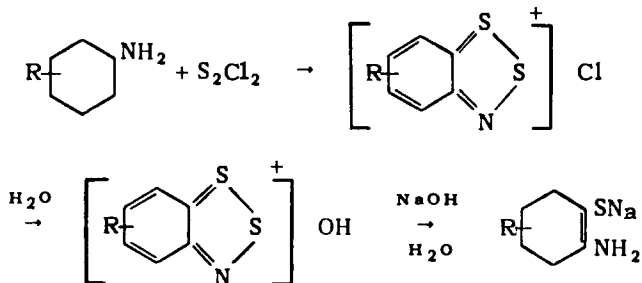
Yields are often less than theoretical. The critical point in the stages of the reaction is the formation of sulfinic acid, which undergoes disproportionation

to sulfonic acid not reducible to mercaptan. Yields may be improved by carrying out the reduction in the cold as long as free sulfinic acid is present; or use of an acid solution is avoided in the reduction to sulfinic acid.

The preparation of dimercaptanaphthalenes, and other dimercapto compounds involves difficulties.³⁰² 1,5-Dimercaptanaphthalene has been prepared successfully by acetylating the mercapto compound as it is formed, and subsequently hydrolyzing the resulting thioacetic ester.³⁰³

Difficulties are encountered also in the anthraquinone series. Reaction of the sulfochlorides with alkali sulfides in the cold gives sulfinic acids; on the other hand, reaction in the warm gives anthraquinone mercaptans in good yield.³⁰⁴ Anthraquinone-1-mercaptans are obtained in good yield from the corresponding sulfochlorides by reduction with dithionate.³⁰⁵

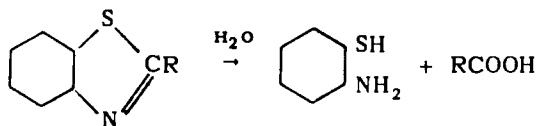
The *Herz process*²⁸² for the synthesis of o-aminothiophenols involves the interaction of primary aromatic amines, their salts or N-acetyl derivatives with sulfur monochloride. Hydrolysis of the resulting chloro compound followed by saponification with caustic yields the sodium salt of the amino thio phenol:



The reaction may be carried out in an indifferent solvent.

There is a strong tendency toward nuclear chlorination during the first stage of the synthesis, particularly in the position *para* to the amino group. This tendency is so marked that chlorination at the *para* position may take place even when this position is occupied by a nitro, carboxyl, or sulfonic group.

o-Aminothiophenols may be prepared through hydrolytic cleavage of benzo-thiazoles:³⁰⁶

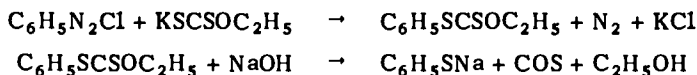


Cleavage may be brought about by alkaline fusion. o-Aminophenylmercaptan may be obtained, for example, by holding at the fusion temperature for 10 to 15 minutes a mixture of 2-phenylbenzothiazole with a fourfold weight of potassium hydroxide moistened with a little water.³⁰⁷ Cleavage may be achieved by refluxing the benzothiazole with 60% aqueous potassium hydroxide.³⁰⁸ The addition of a reducing agent such as sodium sulfide, sodium dithionate, or zinc dust, improves the yield.

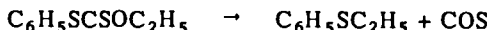
The preparation of 2-amino-5-methylthiol may be considered as illustrative of the procedure: A mixture of 50 grams of 2-amino-6-methylbenzothiazole with 500 cc 50% potassium hydroxide is refluxed six hours, then filtered, cooled and an aqueous solution of 50 gm zinc chloride is added to precipitate the thiophenol as the zinc salt. The latter is filtered, washed with water and dissolved in 400 cc hot 12% hydrochloric acid to liberate the free mercaptan. On cooling, the thiophenol crystallizes out; it is filtered, washed with alcohol and ether and is air dried.³⁰⁹

Thiophenols have been obtained by ring rupture from thionaphthenes by the action of sodium and alcohol, or by heating at 300 to 310° with potassium hydroxide.³¹⁰

A satisfactory method of preparation of thiophenols is offered by *Leuckart's diazo reaction*.¹³³ The diazo compound is first converted to an aromatic xanthic ester, and this is heated with caustic to obtain the desired thiophenol in the form of its alkali metal salt:



When the xanthic ester is heated alone, it decomposes to a disulfide and carbon oxysulfide:



In carrying out the reaction great care should be exercised, since the slightest deviation from the optimum conditions may have an important effect on its course. The reaction proceeds smoothly, but on occasions violent *explosions* have occurred.¹³⁴

The diazo group in aromatic compounds may be replaced directly by heating with hydrogen sulfide.

Thiophenols result on distilling a mixture of the potassium salts of aromatic sulfonic acids and potassium acid sulfide.¹³⁵ The replacement of halogen atoms in aromatic halo compounds by an SH group may be accomplished by heating a mixture of the halo compound and potassium acid sulfide in the presence of copper sulfate. Thiosalicylic acid has been obtained by this procedure from *ortho* chlorobenzoic acid. It is necessary to heat the reaction mixture to 150-200°, and finally at 250° for a short time.²⁸³ Nitrohalobenzenes, such as 1-chloro-2,4-dinitrobenzene, react with particular ease with alkali metal sulfides.¹³⁶ Halogenated aromatic compounds react with hydrogen sulfide at 700° in the presence of certain catalysts to form thiophenols.¹³⁷

Thiophenols are also obtained, though in small yield, by the action of phosphorus pentasulfide on phenols,¹³⁸ and by heating aromatic hydrocarbons with sulfur in the presence of aluminum chloride;¹³⁹ they are obtained also in the form of their halomagnesium salts by the action of sulfur on aromatic halomagnesium compounds.¹⁴⁰

It should be pointed out that contact with thiophenols may result in annoying and stubborn skin irritations.¹⁴¹

Thiophenols may be oxidized to disulfides, most readily by warming with ferric chloride solution. The reverse change may be brought about by mild re-

ducing agents, such as zinc dust and dilute acid. In certain cases the action of dilute alkali is sufficient to bring about the change.²⁸⁴

THIOETHERS

The most generally applicable method for the preparation of thioethers involves the reaction of a sodium mercaptide with an aromatic iodide in the presence of copper powder.¹⁴² Other aromatic halides may also be used, the bromo compounds giving generally satisfactory results when they are made to react with lead mercaptide,¹⁴³ although the method fails occasionally with substituted atyl bromides, as for example, with *o,o*-dimethoxyphenyl bromide. Aromatic thioethers may also be prepared by the interaction of sodium mercaptides with aromatic diazonium chlorides; purely aromatic sulfides are readily obtained by this method.¹⁴⁴ Thioethers may also be obtained through the alkylation of thiophenols by the usual methods. Alkylation may be brought about by the action of alkyl esters of toluene-*p*-sulfonic acid, or a dialkyl sulfate in the presence of about 20% excess of a 15 to 25% solution of caustic soda.²⁸⁵ Aromatic sulfides result when the lead salt of a thiophenol is distilled:



Aromatic thioethers are also formed on heating aromatic mercury compounds with sulfur.¹⁴⁵

Diphenyl sulfide is readily obtained by the oxidation of thiophenol with chromic acid, or in ammoniacal solution, simply by contact with air. It is also formed through the reaction of iodine and sodium thiophenolate, and by heating thiophenol with sulfur.

A few symmetrical amino derivatives of phenyl sulfides and disulfides may be obtained through the reaction of sulfur or sulfur compounds with aniline and its derivatives. For example, *para*-diaminophenyl sulfide, $\text{H}_2\text{NC}_6\text{H}_4\text{SC}_6\text{H}_4\text{NH}_2$, results in good yield on heating aniline and sulfur in the presence of lead oxide.

Thiophenols are converted to disulfides when oxidized under properly controlled conditions.

Reducing agents decompose diphenyl disulfide into two molecules of thiophenol, and alcoholic potassium hydroxide breaks it down into potassium thiophenolate and potassium benzenesulfinate.¹⁴⁶ Chlorine reacting with aromatic disulfides gives aromatic sulfochlorides, ArSCl .¹⁴⁷

SELENOPHENOLS AND TELLUROPHENOLS¹⁴⁸

Selenium, like sulfur, combines with arylmagnesium bromides on heating to form ArSeMgBr , from which selenophenols may be obtained by the action of dilute acids.

Phenyl selenides and tellurides are obtained by heating mercury diphenyl compounds with selenium and tellurium. Diphenyl selenide is formed on heating selenium with diphenyl sulfone; prolonged action of selenium leads to the forma-

tion of diphenyl diselenide, $C_6H_5SeSeC_6H_5$. Phenyl selenhydride, C_6H_5SeH , results on reducing diphenyl diselenide.

Phenyl telluride, $(C_6H_5)_2Te$, results through the reaction of tellurium chloride with mercury diphenyl.

QUINONES

Methods of Preparation

Nearly all derivatives of phenol or aniline can be oxidized to the corresponding *para* quinone, although the yields and ease of oxidation are greatly influenced by substituents in the ring. The yields are generally poor with monohydric phenols and monoamino compounds. On the other hand, quinones are obtained generally in excellent yield from aromatic compounds in which two hydroxyl or two amino groups, or an amino and a hydroxyl group occupy *para* positions. A halogen in the *para* position with respect to an amino or a hydroxyl group also usually improves the yield of quinone. A mixture of sodium or potassium dichromate with dilute sulfuric acid is generally employed as the oxidizing agent.¹⁴⁹

When an amine is used as the starting material, the compound is usually dissolved in dilute sulfuric acid and the dichromate is added gradually. The reaction is generally carried out at or below 20° . The dichromate is sometimes added all at once. The time required for complete oxidation may vary, according to the compound, from less than an hour to two days or more.

Manganese dioxide may be used effectively for the preparation of quinones from simple amines and certain other types of compounds. The quinone can usually be obtained in the crystalline form in the distillate on distilling a mixture of the amine with manganese dioxide and dilute sulfuric acid.

Oxidation proceeds well with alkyl phenols. Occasionally an alkyl group in the *para* position with respect to the hydroxyl or amino group is removed with the formation of a quinone; for example, *m*-xyloquinone results when aminomesitylene is oxidized.¹⁵⁰

Oxidation of hydroquinones to quinones has been effected by use of ferric chloride, chromic acid-sulfuric acid mixture, silver oxide, and manganese dioxide. In a few instances benzoquinone in boiling ethanol has been employed. Since diarylhydroquinones are only slightly soluble in water, oxidation should be carried out in organic media. A solution of ferric chloride or chromic anhydride in acetic acid may be employed for the purpose, or one of quinone in boiling alcohol. Many substituted hydroquinones have been successfully oxidized to the corresponding quinones with silver oxide.¹⁵¹

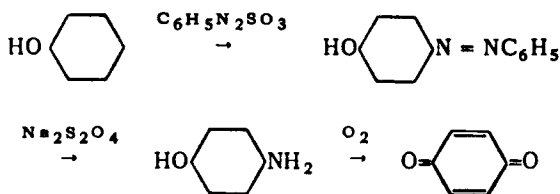
Anthraquinone has been prepared from anthracene by oxidation with sodium chlorate in the presence of vanadium pentoxide.²⁸⁶

Lead dioxide has been used to oxidize 2,6-dihydroxynaphthalene to amphinaphthoquinone,³¹¹ and 2,2'-diaminodiphenyl to diphenoquinone-(2,2').³¹² Many polyhalonaphthalenes and -naphthols have been oxidized with nitric acid to polyhalonaphthoquinones. In these reactions, one or two halogen atoms are generally removed from the molecule of the halo compound and are replaced

by oxygen. 5,6,7,8-Tetrachloronaphthoquinone-(1,4) has been obtained by this method from 1,2,3,4,5-pentachloronaphthalene, and 2,3,6,7-tetrabromonaphthoquinone from 2,3,4,6,7-pentabromo-1-hydroxynaphthalene, the latter by oxidation with nitric acid of density 1.15.³¹³

The Diazo Coupling Method¹⁵²

A very satisfactory method of preparation of *para*-quinones is via the diazo compound obtained by coupling a monohydric phenol with benzene diazonium sulfite. The azo compound is first reduced to the amino phenol and this is subsequently oxidized to the quinone:



The coupling should be carried out in strongly alkaline solution, and sufficient time should be allowed for the completion of the reaction. Ferric chloride is a satisfactory oxidizing agent, but ferric sulfate should be employed where there is possibility of chlorination of the benzene ring by ferric chloride. The ferric salt is added to the aqueous solution of the amine or its salt, and the mixture is steam distilled immediately. The distillation is carried out under vacuum if the quinone is unstable. Coupling and reduction may be carried out successively without isolation of the intermediate azo compound, and the crude amine may be oxidized without purification. The overall yields are high and range from 60 to 95% of theoretical.

This method is particularly satisfactory for the preparation of alkylated quinones. Even quinones with an unsaturated side-chain, such as allyltrimethylquinone, have been obtained in satisfactory yield by this method.

Quinones have been prepared from monohydric phenols by nitrosation followed by reduction to amine and subsequent oxidation.¹⁵³ Quinones have also been prepared from certain *p*-dinitro compounds, by reduction with stannous chloride and hydrochloric acid, and oxidation of the resulting diamino compound with ferric chloride.¹⁵⁴

Some 2,6-disubstituted quinones have been obtained through the oxidation of the corresponding 4-nitrophenol with an equivalent of lead tetraacetate in acetic acid at room temperature.¹⁵⁵

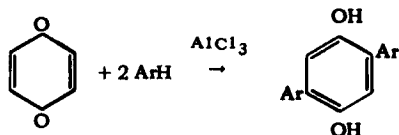
Ortho-quinones are prepared from the corresponding catechols. Silver oxide is a satisfactory oxidizing agent for the purpose and gives good yields of even the highly unstable *ortho*-quinones such as tetramethyl-*o*-quinone.¹⁵⁶ It is sufficient to shake the catechol at room temperature with freshly precipitated

silver oxide in anhydrous ether in the presence of a dehydrating agent, such as anhydrous sodium sulfate.¹⁵⁷ *Ortho*-diamines are not satisfactory starting materials for the preparation of *ortho*-quinones.¹⁵⁸

The more stable highly halogenated quinones may be prepared by oxidizing the corresponding catechols with nitric acid in acetic acid or ethanol solution.¹⁵⁹

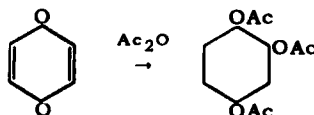
A few amino-*o*-quinones have been prepared by the oxidation of the corresponding aminocatechol in ammoniacal solution by atmospheric oxygen.¹⁶⁰

Aryl hydroquinones may be prepared by condensation of quinone with benzene or other aromatic hydrocarbons.¹⁶¹ Condensation can be brought about by use of aluminum chloride as a catalyst, but occasionally 10% sulfuric acid has been used.



Higher alkylated quinones may be prepared by Clemmensen reduction of acylated hydroquinone dimethyl ethers and subsequent demethylation of the resulting dialkyl hydroquinone dimethyl ether.¹⁶²

Hydroxy hydroquinones may be prepared from quinones by treatment with a mixture of acetic anhydride and sulfuric acid, whereby a triacetoxybenzene is formed:



Hydrolysis of this compound yields the hydroxy hydroquinone. The latter is readily converted to hydroxyquinone on oxidation with ferric chloride.¹⁶³

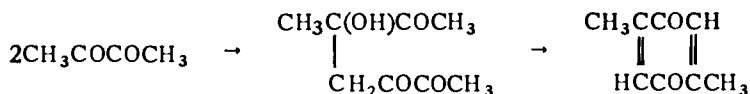
Methoxy- and alkoxyquinones may be prepared through the oxidation of the appropriate polyalkoxy benzene with nitric acid in ethanolic or acetic acid solution.¹⁶⁴ The triethyl ether of pyrogallol is much more resistant to oxidation and more susceptible to nitration than the trimethyl ether.

Methylmercaptoquinone has been prepared by the oxidation of the aminophenol with chromic acid,¹⁶⁵ and several alkylmercaptoquinones have been prepared by oxidizing the corresponding hydroquinones with ferric chloride.¹⁶⁶

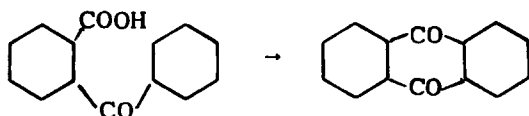
Attempts to prepare naphthoquinones other than α -, β - and *aphi*-naphthoquinones have resulted in the formation of diquinones containing dinaphthyl residues.²⁹⁷ Of the six theoretically possible anthraquinones only 1,2-, 1,4-, and 9,10-anthraquinones are known.

Chromans may be oxidized to quinones in good yield by ferric chloride or silver nitrate in ethanolic solution.¹⁶⁷ Ethanolic silver acetate would appear to be a more satisfactory oxidizing agent.

Quinones are formed through the condensation of 1,2-diketones:¹⁶⁸



The condensation of *o*-carboxy diaryl ketones to quinones is a method of wide applicability. Cyclization of *o*-benzoylbenzoic acids to anthraquinones may be brought about effectively by the action of phosphoric acid:²⁹¹

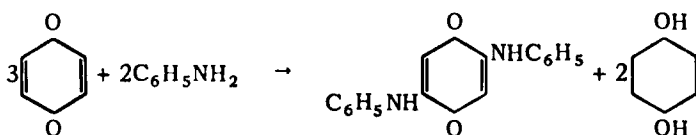


Quinone chlorimides are formed through the action of a solution of chloride of lime on *para*-aminophenols.¹⁶⁹ Quinone monoanilide, $O=C_6H_4=NC_6H_5$, results through the oxidation of *p*-hydroxydiphenylamine. Quinone dianilide, $C_6H_5N=C_6H_4=NC_6H_5$, results through the oxidation of diphenyl *p*-phenylenediamine, $C_6H_5NHC_6H_4NHC_6H_5$.

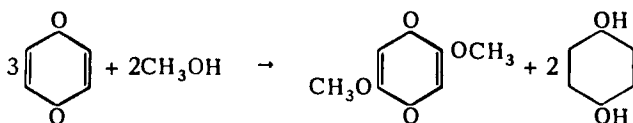
Simple mononuclear *ortho*-quinones in the monomeric form are not known, but mononuclear halo *ortho*-quinones have been prepared.¹⁷⁰ Simple quinone imides of the type of $O=C_6H_4=NH$ and $HN=C_6H_4=NH$ are also unknown.¹⁷¹

Behavior and Reactions of Quinones

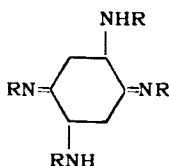
Quinones of the type of benzoquinone and naphthoquinone, which have double bonds adjacent to the carbonyl group, are distinctly reactive. Their reactivity surpasses that of open chain α,β -unsaturated ketones. They form addition compounds with many hydrogen compounds.¹⁷² With aniline and benzoquinone, for example, dianilinoquinone is obtained together with two molecular equivalents of hydroquinone:¹⁷³



Other aromatic amines react similarly. Nitrated aromatic amines give mono-aminoquinones. With naphthoquinone and aniline, molecular equivalents of 2-anilino-1,4-naphthoquinone and 1,4-dihydronaphthalene are formed. A similar reaction takes place with methanol in the presence of zinc chloride; with benzoquinone 2,5-dimethoxybenzoquinone is formed:¹⁷⁴

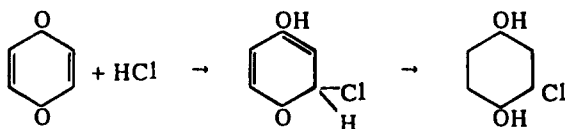


Azophenines



are formed by the reaction of hydrochlorides of aromatic amines with quinones or compounds related to quinones such as quinone oximes, nitrosoamines, aminoazo compounds, etc.¹⁷⁵

Direct addition to the quinone molecule is apparently of 1,4-type, addition of hydrogen chloride resulting in the formation of monochlorohydroquinone:¹⁷⁶



Some hydroquinone is also formed in this reaction, and condenses with quinone to form quinhydrone. When the halo hydroquinone is oxidized to halo quinone and this is made to react with halogen again, a dihalo hydroquinone is formed. By repeated oxidation and halogenation, tetrahalohydroquinone is finally obtained.

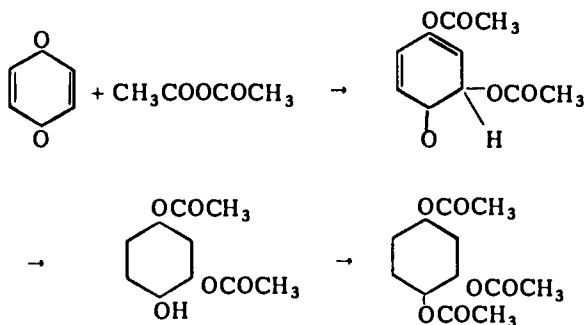
This type of addition is observed also with hydrocyanic acid, mercaptans, sulfinic acids, malonic ester and in general with compounds containing a reactive methylene group. Benzene also gives similar addition compounds with quinones in the presence of aluminum chloride. It is possible to prepare addition compounds with two or four atoms of halogens.¹⁷⁷ Benzoquinone combines readily with benzenesulfinic acid in aqueous solution to form hydroquinone-2,5-diphenylsulfone; thymoquinone and β -naphthoquinone behave in like manner.¹⁷⁸ Quinone reacts with neutral sodium sulfite, giving hydroquinone monosulfonate in quantitative yield; this is partially hydrolyzed to hydroquinone and hydroxyquinone.¹⁷⁹ Sodium bisulfite reacts with α - and β -naphthoquinone to form sulfonic derivatives of the dihydroxynaphthalenes. Thio acids also combine with quinone to give thio acid substitution derivatives of hydroquinone.¹⁸⁰ Potassium hydrogen sulfide reacts with quinone in carbon disulfide solution to form

the potassium salt of benzoquinoneoxonium hydrosulfite, $\text{O} = \text{C}_6\text{H}_4 = \text{O} \begin{matrix} \text{H} \\ \diagup \\ \text{SK} \end{matrix}$

Benzoquinones, reacting with hydrogen cyanide, yield cyanoquinols and not cyanohydrins,¹⁸¹ phenanthraquinone gives a dicyanohydrin.¹⁸²

Benzoquinones combine with phenols to form well-defined molecular compounds.¹⁸³ They react with two molecular equivalents of a monohydric, and one molecular equivalent of a dihydric phenol, although a few exceptions are known. Quinhydrone, $\text{OC}_6\text{H}_4\text{O}(\text{HOC}_6\text{H}_4\text{OH})$, results, for example, when cold aqueous solutions of hydroquinone and *p*-benzoquinone are mixed. Molecular compounds are formed also through the reaction of benzoquinones with aromatic hydrocarbons.¹⁸⁴

Acetic anhydride combines with quinone under the catalytic influence of sulfuric acid. The addition is followed by a molecular rearrangement to a phenol which is subsequently acetylated, the reaction proceeding at 50° with benzoquinone:



This is known as the *Thiele reaction*.²¹⁹ The products obtained from α - and β -naphthoquinones, when these are subjected to the Thiele reaction, are identical.

2-Alkyl-1,4-naphthoquinone undergoes the reaction readily in the presence of perchloric acid as a catalyst. 2,5-Dimethoxyquinone fails to undergo this reaction, while 2,5-dimethylquinone reacts very slowly.

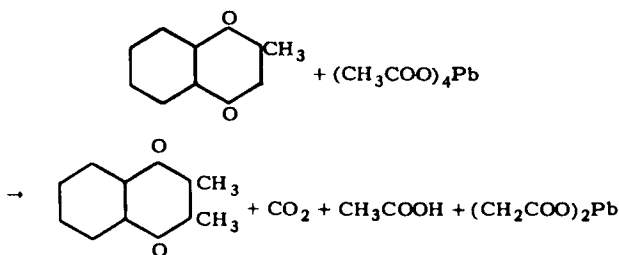
A methyl group in the 2-position exerts a retarding effect on substitution reactions. Sulfhydryl compounds, HSR, constitute an exception, however, and rapidly add to 2-methyl-1,4-naphthoquinone.

While anthraquinone ionizes as a nonacid base in sulfuric acid, derivatives of anthraquinone with a methoxy group α to each carbonyl group react as diacid bases.²⁹²

Quinone and naphthoquinone give diene adducts in the Diels-Alder reaction.

Alkylation with Lead Tetraacetate

2-Methyl-1,4-naphthoquinone is methylated rapidly when heated under reflux with three to four molecular equivalents of lead tetraacetate:



The reaction is promoted by methanol or malonic acid.

The reaction may be carried out with other lead tetraacylates, and the latter need not be employed in the preformed state; it is generally sufficient to heat the quinone with a mixture of the fatty acid, red lead and a promoter. The isopropyl, benzyl and *n*-heptyl groups have been introduced in the 3-position in 2-methyl-1,4-naphthoquinone by this procedure by use of isobutyric, phenylacetic and caprylic acids.

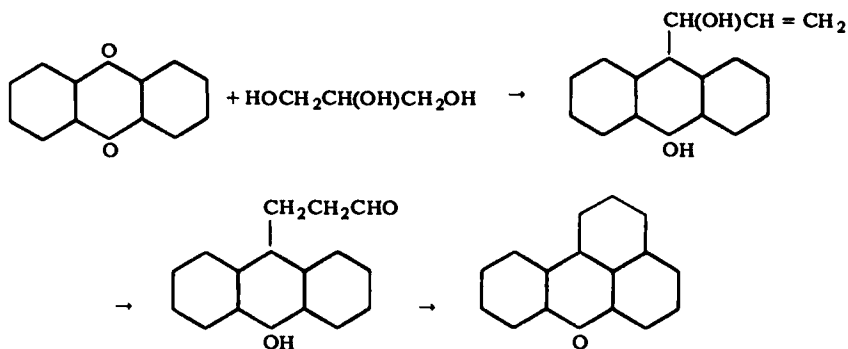
This reaction proceeds readily also with diacyl peroxides which are obtained from the corresponding acid chlorides or anhydrides by reaction with cold aqueous sodium peroxide in the presence of ether or petroleum ether. The latter extracts the sensitive acyl peroxide as it is formed.

The reaction is applicable to hydroxyquinones, such as 2,5-dihydroxy-*p*-benzoquinone.

Anthraquinone differs in many respects from quinones with a true ethylenic linkage; its behavior is essentially that of an aromatic compound. It is not readily sulfonated with concentrated sulfuric acid. The compound may be sulfonated, however, by means of fuming sulfuric acid containing a trace of a mercury salt, the sulfonic group entering the α -position. Nitration can be accomplished by use of mixed acids under forced conditions, when, again, the α -position is first attacked. Halogens attack the compound with great difficulty, and halogenated anthraquinones are prepared by indirect methods. Anthraquinone is resistant to oxidation under very drastic conditions. The compound fails to undergo the Friedel-Crafts alkylation or acylation reactions.

Leuco compounds of hydroxyanthraquinone react readily with aldehydes, $RCHO$, in aqueous alkaline solution in the presence of sodium acid sulfite, the group RCH_2 entering the ortho position with respect to the hydroxyl group.¹⁸⁵ Aminoanthraquinones react similarly with formaldehyde and formaldehyde-bisulfite compound. These condensations should be carried out under a nitrogen atmosphere.

Anthraquinone reacts with glycerine in the presence of sulfuric acid to form a hydroxyanthracene derivative with an unsaturated alcohol residue substituent at 9-position; this residue isomerizes to an aldehyde group and finally an intermolecular condensation gives mesobenzanthrone:¹⁸⁶



This is known as *Bally's reaction*.

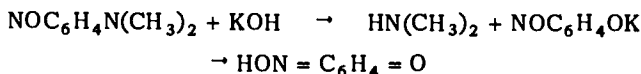
Reaction of Quinones with Phenylhydrazine and Hydroxylamine

Benzoquinone and its homologs are reduced to hydroquinones by *phenylhydrazine* or methylphenylhydrazine, but α - and β -naphthoquinone react with phenylhydrazine to form condensation products, α -naphthol giving benzeneazo- α -naphthol.¹⁸⁷ Nitrophenylhydrazines condense with benzoquinone giving hydroxyazocompounds. Acylated phenylhydrazines of the type of $C_6H_5N(Ac).NH_2$ also give hydrazones; these undergo rearrangement, forming acyl derivatives of hydroxyazocompounds when their ethereal solutions are treated with solid potassium hydroxide.¹⁸⁸ The products of the reaction of unsymmetrical acylphenylhydrazine and β -naphthoquinone are probably O-acylated azonaphthols;¹⁸⁹ but α -naphthoquinone reacting with *unsym-benzoyl*- and methylphenylhydrazine gives monohydrazones. Benzoquinones react with semicarbazide hydrochloride apparently giving azo compounds.²⁹⁸

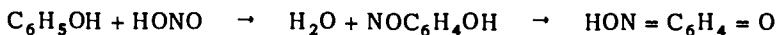
Free *hydroxylamine* causes the reduction of benzoquinones to quinols; oximes are formed, however, when the quinones are made to react with aqueous alcoholic solutions of hydroxylamine hydrochloride.¹⁹¹ The reactivity of the quinone toward hydroxylamine hydrochloride is markedly decreased when both *ortho* positions bear alkyl groups or halogen atoms as substituents. Thus, while both monoximes and dioximes may be obtained from quinones bearing such substituents in 1 and 5 positions, 1,6-disubstituted and trisubstituted quinones give only monoximes, while tetrasubstituted quinones fail to give an oxime.¹⁹²

Quinones differ widely in their ability to form oximes. No oximes have been obtained from trichloroquinones and tetra substituted quinones such as chlor- and bromanils, and dibromothymoquinone. Only monoximes have been obtained from 2,6-dichloro- and dibromobenzoquinones.²⁹⁹ *p*-Xyloquinone and 2,5-dichloro-*p*-benzoquinone both give mono and dioximes. Anthraquinone is highly resistant to the action of hydroxylamine hydrochloride,¹⁹³ and a monoxime is formed only upon heating it with an alcoholic solution of the hydrochloride of the base. Mono- and dioximes of acenaphthoquinone and phenanthraquinone have been prepared.¹⁹⁴ When naphthoquinone is treated with hydroxylamine, the principal product is the 1-keto-2-oximino derivative, but when 4-phenylamino-1,2-naphthoquinone is treated similarly, the dioximino product is obtained.²⁸⁷

Quinone monoximes are formed when nitroso derivatives of tertiary aniline bases are heated with aqueous alkalis:¹⁹⁵



They are obtained also through the reaction of phenols with nitrous acid.



Ortho quinones condense with diamines containing primary amino groups with elimination of water to form cyclic compounds.

Reduction of Quinones; Other Reactions

Quinones in general are reduced more or less readily to hydroquinones by the action of *sulfurous acid*, or by aqueous *sulfur dioxide*. *p*-Benzoquinone, aminophenanthroquinone, *o*-naphthoquinone and phenanthraquinone are readily converted to the corresponding hydroquinones with sulfur dioxide. Benzoquinone is not converted quantitatively to hydroquinone by this reagent, but approximately 20% of the compound is obtained as quinolsulfonic acid.¹⁹⁷ Substituted quinones may also be reduced with sulfur dioxide. Chloranil, for example, may be converted to the corresponding hydroquinone by twice saturating its aqueous suspension with sulfur dioxide at intervals of 24 hours.¹⁹⁸ In certain instances reduction is best effected by heating an alcoholic solution of the quinone with sulfurous acid in a sealed tube at 100°.¹⁹⁹ Quinone is reduced quantitatively, even in the cold, by titanous chloride and hydrochloric acid to hydroquinone.¹⁹⁶

Sodium hydrosulfite is an excellent reducing agent for such quinones as β -naphthoquinone and phenanthraquinone, which resist the action of sulfur dioxide.

Many other reducing agents have been used for the conversion of quinones to hydroquinones; among these are *titanium trichloride*,²⁰⁰ *phenylhydrazine*,²⁰¹ *stannous chloride* and *dilute hydrochloric acid*,²⁰² *zinc dust* and *acetic acid*, *tin* and *hydrochloric* or *acetic acid*,²⁰³ *zinc dust* and concentrated aqueous *sodium hydroxide*²⁰⁴ or *ammonia*, powdered *aluminum* and *sulfuric acid*,²⁰⁵ *iron* and *hydrochloric acid*, or *iron* and *ferrous chloride*,²⁰⁶ *potassium nitrosodisulfonate*, $(\text{KSO}_3)_2\text{NO}$,²⁰³ and alkaline *hydroxylamine*.²⁰⁷ The last named is a particularly effective reducing agent, and reacts with considerable evolution of heat.

Certain substituents in the ring in the immediate vicinity of the carbonyl group in quinones influence the susceptibility of the group to reduction. Thus, while 1,4-dimethylantraquinone may be reduced with alkaline hydrosulfite, 1-methyltolylantraquinone is not affected by this reagent.²⁰⁸

α -Naphthoquinone and diphenokinones are reduced satisfactorily with stannous chloride and dilute hydrochloric acid.²⁹⁶ Phenanthraquinone is readily and quantitatively converted to phenanthrahydroquinone by treatment with zinc dust and acetic acid, or stannous chloride.²⁰⁹

The reduction of quinone to hydroquinone on the commercial scale would seem to be best carried out by first converting the quinone to quinhydrone, and then reducing the latter by the addition of a ferrous salt and calcium carbonate. Reduction of quinhydrone may also be carried out with iron and water.²¹⁰

Anthrahydroquinone is an unstable compound, and is best prepared as its diacetyl derivative through the reduction of anthraquinone with zinc dust in the presence of acetic anhydride and sodium acetate. This procedure may be employed also for the preparation of the diacetates of other unstable hydroquinones. The dihydic phenol is obtained by the action of sodium hydrosulfite on anthraquinone. Other products are formed under more vigorous conditions; tin and hydrochloric acid reacting with an acetic acid solution of the quinone give anthranol, together with some dianthryl.²⁹⁵

The reduction of α -benzoylantraquinone with aluminum and concentrated sulfuric acid or zinc dust and ammonia leads to the formation of strongly fluorescent products with a deep violet color,²¹¹ which appear to be compounds with a trivalent carbon atom, and behave as inner complexes.²¹²

Quinoid indophenols may be reduced by heating their aqueous suspensions with a concentrated solution of sodium sulfide,²¹³ $\text{H}_2\text{NC}_6\text{H}_4\text{N} = \text{C}_6\text{H}_4 = \text{O}$ giving, for example, $\text{H}_2\text{NC}_6\text{H}_4\text{NHC}_6\text{H}_4\text{OH}$. The quinoid dyes of the triphenylmethane series are reduced to leuco compounds, almost without exception, when treated with a concentrated solution of sodium sulfide, or with tin and hydrochloric acid.²¹⁴ The parent compound of this group, namely diphenylquinomethane, is readily converted to *p*-hydroxytriphenylmethane by treatment with zinc and acetic acid:²¹⁵

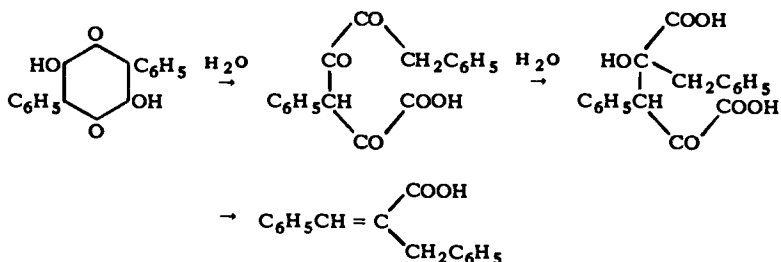


Anthraquinone is not affected by sulfur dioxide; reduction of this quinone under more vigorous conditions results in the formation of anthranol, dianthryl²¹⁶ and dianthrol. The latter is formed when reduction is carried out with zinc dust and 10% caustic solution at 100° under pressure.²¹⁸ Dianthrol is converted to dianthrone on oxidation. Anthraquinone is readily reduced to the corresponding dihydic phenol by treatment

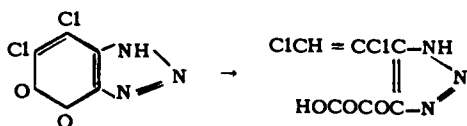
with sodium hydrosulfite; anthraquinol is also obtained by digesting the quiaone with zinc dust and sodium hydroxide. The dihydroxy compound is reconverted to the quinone when shaken with air in the presence of excess sodium hydroxide. Anthraquinone may be reductively acetylated to anthraquinol diacetate. Reduction does not proceed beyond the quinol stage when well dried zinc dust and acetic anhydride free from acetic acid are used.²⁹⁴ The reaction may be employed to prove the presence of a quinone grouping. Anthraquinone is reduced to anthracene when heated at 150° with hydriodic acid or zinc dust and ammonia.

Quinones undergo polymerization with comparative ease, and oxidation in alkaline solution gives brown amorphous substances resembling humic acid.²¹⁷ The formation of a derivative of the diphenyl series through the union of two quinone ring systems would appear to be the first stage in the polymerization.

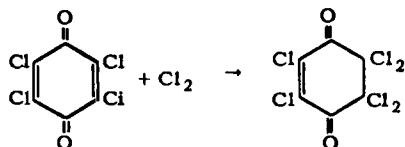
Dihydroxyquinones undergo a characteristic fission when treated with alkalis. The 2,4-diphenyl derivative yields the isomeric α -benzylcinnamic acids, following a benzylic rearrangement of the original product of fission:



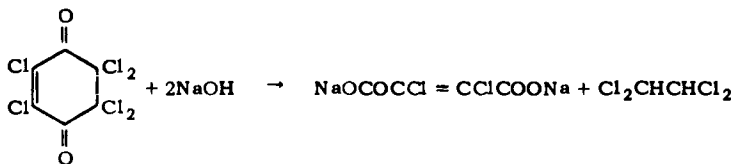
6,7-Dichlorobenzotriazole-4,5-quinone undergoes ring rupture under the action of alkalis, giving 5-[(α,β -dichlorovinyl)-V-triazolyl-4]glyoxylic acid:



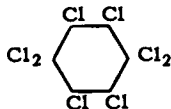
Chloranil heated with manganese dioxide and hydrochloric acid gives hexachloro-cyclohexanedione:



The hexachloro compound undergoes ring rupture when heated with alkalis, forming the alkali metal salt of dichloromaleic acid and *sym*-tetrachlorethane:



Hexachlorobenzene results on strongly heating a mixture of chloranil with phosphorus trichloride and phosphorus pentachloride. If the reaction is carried out at 130-140°, the primary product is hexachlorobenzene dichloride,



References

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2. Woroshov, *Chem. Zentr.* 1934 II, 2523; *French patent* 709,184 and 720,720.
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CHAPTER 24

AROMATIC CARBONYL COMPOUNDS

AROMATIC ALDEHYDES

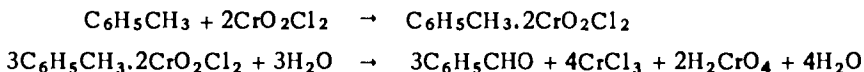
Methods of Preparation

The principal methods utilized for the preparation of aromatic aldehydes may be divided in two main categories: those directed toward the conversion of a group or a part of a group already present in the molecule to a formyl group, and those aiming at the introduction of the aldehyde group into the aromatic nucleus. Among the first are the methods based on the oxidation of a methyl, carbinol, or a halomethyl group attached to the nucleus; those based on the partial reduction of an acid chloride, or other derivative of an acid, and a nitrile; and certain other methods utilizing aromatic olefinic compounds and aromatic acids. In the second category are methods based on the condensation of such compounds as chloroform, carbon monoxide, hydrocyanic acid, etc., with aromatic compounds in the presence of the appropriate condensing agents. Reactions involving the use of Grignard reagents in connection with aromatic nitriles or esters also belong in this category.

Oxidation of Methyl or Other Alkyl Groups – Étard's Reaction

Methyl groups joined to an aromatic nucleus may be oxidized by various agents; a mixture of manganese dioxide and sulfuric acid, manganese sulfate, ceric oxide and sulfuric acid¹ have been used for the purpose. Copper sulfate has sometimes been added to the reaction mass when a mixture of manganese dioxide and sulfuric acid is used as the oxidizing agent.²

The most important method of conversion of a methyl group in an aromatic compound to an aldehyde group is that originated by Etard.³ In this method, *chromyl chloride* is used as the oxidizing agent. A complex is formed between the aromatic compound and two molecular proportions of chromyl chloride, which is subsequently decomposed by treatment with water:



The procedure is to add two equivalents of chromyl chloride in solution in carbon disulfide, in portions and with caution, to one equivalent of the hydrocarbon. The temperature of the reaction mixture is kept between 25° and 45°. The red color of the reagent is gradually discharged and a chocolate-brown crystalline solid separates out. On treatment with water, this solid decomposes to the aldehyde and chromic chloride and chromic acid. The aldehyde is recovered by steam distillation or by extraction with a solvent.

The aldehyde must be isolated rapidly to prevent losses due to decomposition. Decomposition may also be avoided by destroying the chromic acid formed in the reaction with sulfur dioxide.

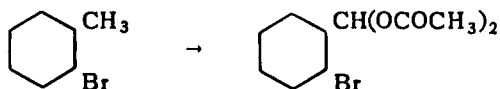
In *Bornemann's modification* of *Étard's method*, a solution of somewhat less than two molecular equivalents of chromyl chloride in carbon disulfide is added gradually to one of a molecular equivalent of the aromatic compound in the same solvent. The mixture is cooled if any considerable amount of heat is evolved during the addition of the reagent, and time is allowed after each addition for the complete separation of the chromyl chloride complex. The mixture is allowed to stand for a time after the addition of all of the chromyl chloride solution, and the complex is then filtered and freed of all carbon disulfide by gently warming under vacuum. Finally the complex is decomposed with water, and the aldehyde is isolated immediately.

It must be pointed out that the solid chromyl chloride complex is *explosive*, and grave risks of dangerous explosions are involved in this modification of the method when working with comparatively large quantities.

Yields of aldehyde may be as high as 80% when the correct experimental conditions are followed closely, but even small deviations from these conditions may result in lowered yields.

Aromatic compounds with alkyl groups containing more than one carbon atom, subjected to this reaction, are converted to a mixture of ketone and aldehyde. Ethylbenzene, for example, gives acetophenone and benzaldehyde, although propylbenzene yields benzyl methyl ketone as the principal product.⁴

A methyl group attached to an aromatic nucleus may also be oxidized by treatment at 5-10° with a mixture of chromic acid and acetic anhydride, sulfuric acid, and acetic acid.⁵ In this reaction the aldehyde is obtained as the *gem* diacetate, which is not oxidized further by the chromic acid mixture:



The diacetate may be converted to the aldehyde by hydrolysis with acid. This procedure is known as the *Thiele-Winterstein method*.

Alkyl benzenes have been oxidized electrolytically to aldehydes,⁶ and also catalytically with oxidizing gases in the presence of molybdenum, uranium, or copper oxide.⁷

Activated methyl groups may be oxidized to a formyl group by treatment with *selenium dioxide*; phenyl glyoxal, for example, can be readily obtained by this method from acetophenone.⁸

Elemental selenium separates out and water is the only other product formed; isolation of the aldehyde, is therefore, a simple matter. *Glassy* selenium may be formed during the reaction; selenium in this form reacts more vigorously with nitric acid, and may cause an explosion when one attempts to reconvert it to oxide.

Nitrotoluenes, treated with an aqueous alcoholic solution of sodium sulfide, or a solution of sulfur in concentrated sodium hydroxide, are converted to amino aldehydes by a process of reduction and oxidation within the molecule. The yields are good, but occasionally aldehydes are not produced, and sometimes toluidines and aminobenzoic acids are obtained as the principal products.⁹

Methyl groups activated by nitro groups in the ortho or para position readily condense with nitrosobenzenes to give Schiff bases, which may be hydrolyzed to the corresponding aldehydes.¹⁰ The overall yields are generally good.

The methyl group in acetophenone is capable of reacting with amyl nitrite in the presence of sodium ethoxide to form isonitrosoacetophenone,

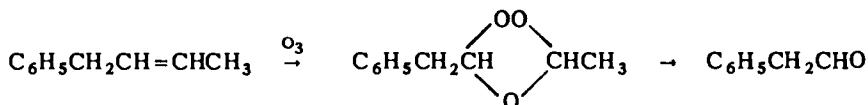


This compound, converted to its bisulfite derivative and hydrolyzed with dilute sulfuric acid, gives phenylglyoxal, $\text{C}_6\text{H}_5\text{COCHO}$.¹¹

Oxidation of methylene groups to carbonyl groups may be accomplished by use of nitrous gases.²⁵² This method is suitable for the preparation of larger quantities of ketones. It has been employed for the preparation of mesoxalic ester.

Aldehydes by Ozonolysis

Aromatic aldehydes may be obtained from aromatic compounds having an unsaturated side chain by ozonization followed by decomposition of the ozonide:¹²



Aldehydes have been obtained through the oxidation of naturally occurring unsaturated aromatic compounds; thus anisaldehyde has been prepared from anethol and vanillin from isoeugenol.

As an example the preparation of *vanillin* may be cited: Forty-one grams of isoeugenol in 500 cc chloroform are ozonized for several hours at -10 to -20° ; after removal of the solvent by distillation under vacuum, the ozonide is stirred for 30 min with 100 cc water, 100 gm ice and 20 gm sodium bisulfite. Then 40 gm of sodium bisulfite and 25 gm sodium hydrogen sulfite are added and after the first vigorous reaction has subsided, the mixture is heated at 70° until solution is complete. The bisulfite compound is finally extracted with ether, the extract is washed with bicarbonate solution and the ether removed by evaporation to obtain the crude vanillin in 84% yield.²⁹¹

In the preparation of pyridine-2-aldehyde from α -(2-pyridyl)- β -phenylethylene by this method, reduction of the ozonide is brought about by treating with a suspension of zinc dust in water, containing a little silver nitrate and hydroquinone, at room temperature overnight.²⁹²

Aldehydes may be prepared by ozonolysis from aromatic compounds by rupture of a ring. *o*-Phthalaldehyde and phthaldehyde acid have been obtained in this manner from naphthalene,²⁹³ and 4-ethoxy-2-methoxy-3-ethylsalicylaldehyde has been prepared from 5-ethoxy-3-methoxy-4-ethylcoumarin.²⁹⁴ The method is applicable to the preparation of polynuclear aldehydes, such as fluorene-1-aldehyde from fluorenone, anthraquinone-1-benzaldehyde from benzanthrene,²⁹⁵ and phenanthrene-4-aldehyde-5-carboxylic acid from pyrene,²⁹⁶ in yields varying between 30 and 40%.

Phenanthrene-4-aldehyde-5-carboxylic acid is prepared by oxidizing a 10% acetic acid solution of pyrene with 5% ozone for fourteen hours, pouring the mixture in water, filter-

ing the precipitate, digesting it twice with 1% aqueous caustic, and oxidizing with a solution containing hypochlorite equivalent to 14% active chlorine.²⁹⁷

Aldehydes by Oxidation of Olefins

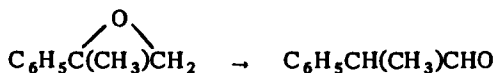
Arylated olefins, and especially propenylbenzenes, $\text{ArCH}=\text{CHCH}_3$, are easily converted to aromatic aldehydes by oxidation. Nitrobenzene is the usual oxidizing agent employed, and the reaction is carried out in dilute alkaline solution.¹³ This method is employed for the preparation of *ortho*- and *para*-hydroxybenzaldehydes on the technical scale; vanillin is also made on the commercial scale from isoeugenol by this method.²⁹⁸ The method is applicable only to the preparation of aldehydes which do not undergo the Cannizzaro reaction and are stable toward oxidizing agents.

Certain aromatic ethylenic compounds may be oxidized to the aldehyde stage with potassium permanganate. Good yields are obtained only when the aldehyde group is protected by negative substituents, preferably at *ortho* position. Aldehydes have been prepared by this method from 4-amino- and 4-chlorostilbene-2-sulfonic and 4,4'-dinitrostilbene-2,2'-disulfonic acid;²⁹⁹ also from *o*- and *p*-nitrocinnamic acids,³⁰⁰ β -(2- and 4-quinolyl)-acrylic acids,³⁰¹ β -chlorostyrenes,³⁰² and 1-(3-sodioquinoline sulfonic acid (2))-2-phenylethylene.³⁰³

γ -Methylquinoline may be converted to quinoline-4-acrylic acid by condensation with chloral, and treatment with alcoholic potassium hydroxide; oxidation with potassium permanganate gives quinoline-4-aldehyde.³⁰⁴

Isomerization of Epoxides

Unsaturated compounds may be converted to epoxides by oxidation with peracids or peroxides. Epoxides may be isomerized by heating to carbonyl compounds; 1-phenyl-1-methylethylene oxide gives an aldehyde:¹⁴

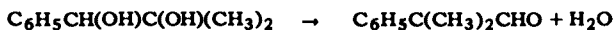


Glycidic acids, $\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{R}'\text{C} \quad \text{CR}''\text{COOH} \end{array}$, are converted to aldehydes or ketones by heating:



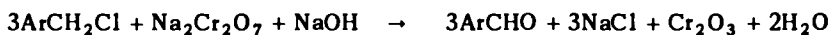
The esters of such acids are obtained through the condensation of ketones, RCOR'' , with halo acids, $\text{R}''\text{CHXCOOR}$, in the presence of sodium ethoxide or sodium amide. The esters are converted to acids by heating with an equivalent of sodium ethoxide in absolute alcohol, and decomposing the resulting sodium salt with an acid. The glycidic esters may be converted to keto esters on heating to a high temperature. Passage of vapors of the glycidic ester over infusorial earth heated at 310° converts them to aldehyde esters.

Related to this transformation is the conversion of certain glycols and iodohydrins to aldehydes. The latter conversion is accomplished by heating the iodohydrins with silver nitrate or mercuric oxide.¹⁵ Secondary-tertiary phenyl ethylene glycols give aldehydes on heating, migration of the phenyl group occurring during the transformation:



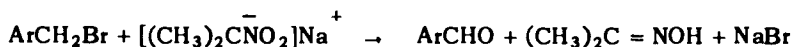
Oxidation of Alcohols and Chloromethyl Derivatives

Aromatic aldehydes may be obtained by the oxidation of primary aromatic alcohols by use, for example, of *meta*-nitrobenzenesulfonic or carboxylic acid in basic solution.¹⁶ This method works especially well with aromatic alcohols in which hydroxyl groups are attached to the aromatic nucleus. Aldehydes may be obtained also through the direct oxidation of monochloromethyl derivatives of the type RCH_2Cl .¹⁷ Oxidation may be accomplished by use of alkali dichromate and caustic:



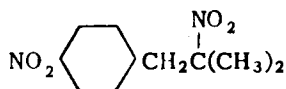
Oxidation may be effected also by boiling with dilute nitric acid, or with a solution of heavy metal nitrates.¹⁸ On the commercial scale benzyl chloride is converted to benzaldehyde by heating with lead nitrate in a carbon dioxide atmosphere.

Oxidation has been effected by the action of sodium 2-propanenitronate, cyclohexanenitronate or other alkyl nitronates. The reaction results in the formation of a nitronic ester. The strong proton affinity of the $-\text{NO}$ group renders the ester very unstable, and an immediate intramolecular redox process takes place with the formation of the aldehyde and an oxime:²⁵³



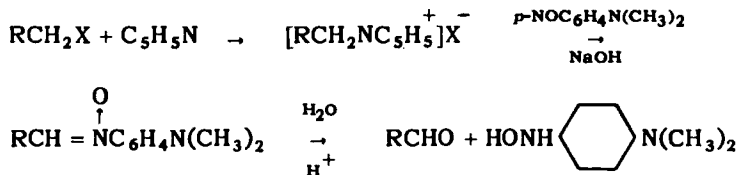
The procedure is as follows: A mixture of molecular equivalents of the nitro compound, the benzyl halide and alcoholic sodium ethoxide is allowed to stand for 15 hours at room temperature. The greater portion of the alcohol is then distilled off under vacuum, and the residue is poured in water. A little caustic is added to hold the unreacted nitro compound in solution, and the aldehyde is isolated by the appropriate procedure.²⁵⁹

Aldehydes have been obtained by this method in yields ranging 68 to 77% with benzyl halides having a methyl, carbomethoxy, cyano or trifluoromethyl group or a bromine atom in the *para* position. *p*-Acetoxybenzaldehyde cannot be prepared by this method, since it undergoes aldol condensation under the reaction conditions; *p*-nitrobenzyl chloride undergoes C-alkylation giving 2-nitropropane and an 83% yield of the compound



Benzyl chlorides may be converted to aldehydes by reaction with phenylhydroxylamine in aqueous or alcoholic pyridine solution, with subsequent conversion of the resulting nitron into the aldehyde and phenylhydroxylamine.²⁶⁰

The halomethyl group may be converted to an aldehyde group by first converting it into the pyridinium salt and reacting this with nitrosodimethylaniline; hydrolysis of the nitron formed gives the aldehyde.²⁶¹

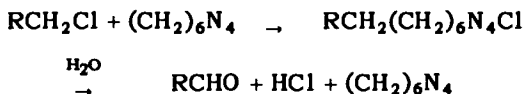


The reaction, named after its discoverer *Kröhnke*, is of wide applicability, and gives good yields of aromatic aldehydes as well as of unsaturated, and α -keto aldehydes and dialdehydes. It is especially suitable for the preparation of sensitive aldehydes.²⁶² The reaction is favored by electron attracting substituents, and even dinitrobenzaldehydes are readily obtained.²⁶³

The methylene groups in *o*- and *p*-nitrobenzyl chlorides are so strongly activated that these compounds may be condensed directly with *p*-nitrosodimethylaniline in alcoholic solution to Schiff bases.²⁶⁴

Sommelet Synthesis²¹

In the Sommelet reaction an aldehyde is formed by the removal of hydrogen halide from benzyl halides and its replacement with oxygen. This is accomplished by causing the halide to react with hexamethylenetetramine in aqueous alcoholic solution. An addition compound is first formed, which is decomposed by water to the expected aldehyde:



The normal *procedure* in carrying out the Sommelet reaction is as follows: The halo-methyl compound is added to a solution of 10% excess hexamine in about seven parts by weight of chloroform, and the mixture is heated under reflux for one to two hours. The mass is then cooled and the solid reaction product is filtered. If the product is appreciably soluble in chloroform, a portion of the solvent is removed by evaporation, ether or acetone is added and the precipitate filtered. Hydrolysis of the hexaminium salt may be effected in water or other hydroxylic solvent, or a mixture of water with an organic solvent. A 60% aqueous acetic acid is a satisfactory medium for the reaction. The solution is heated under reflux for one-half to two hours; then an excess of hydrochloric acid is added and boiling is continued for five minutes in order to hydrolyze the Schiff base.

When dealing with benzyl halides bearing electron attracting substituents, and with aliphatic halides and bishalomethyl compounds, it is necessary to conduct the first stage of the reaction, namely the preparation of the hexaminium salt separately, using a non-aqueous solvent. It is also desirable to isolate the hexaminium salt if the starting halomethyl compounds are not pure.

Aliphatic aldehydes are very sensitive to the conditions of the Sommelet reaction and should be continuously removed by passing steam through the reaction mixture.

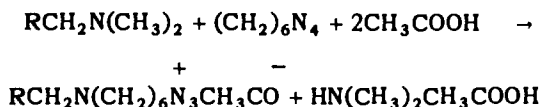
The most important side reaction is the formation of the methylated amine in accordance with the equation:



Yields of aldehydes are good in some instances. Electron attracting substituents decrease the rate of reaction and the yield even when electron releasing

substituents are also present. Phenolic aldehydes are not readily obtainable by this method because the aromatic ring, when activated by hydroxyl groups, tends to condense with formaldehyde. When electronegative groups are present in the phenolic body, they may counterbalance the effect of the hydroxyl groups, and the formation of aldimine may become possible. It is necessary however to block the hydroxyl groups by esterification or etherification. α -Chloroisodurene reacts abnormally to form $\text{CH}_3\text{CH}_2\text{NHCH}_2\text{NHCH}_2\text{C}_6\text{H}_2(\text{CH}_3)_3$.²²

Quaternary ammonium salts of the type involved in the Sommelet synthesis may be obtained by amine exchange from Mannich bases and hexamethylenetetramine in acetic acid solution:²⁵⁴



These bases yield aldehydes on hydrolysis in the usual manner. The method is not of general applicability.

Oxidation of Benzylamines to Aldehydes

Arylamines may be converted to aldehydes by oxidation. Benzylamine, for example, subjected to the action of permanganate in acetone solution at -50° for six hours, gives benzaldehyde in 70% yield.²⁶⁵ Oxidation may be effected with isatin or alloxan.²⁶⁶ Hydroxybenzylamines may be oxidized to aldehydes by passing a current of air through their boiling alkaline solution containing potassium isatin-5-sulfonate.²⁶⁷ The reaction takes place more readily if the aminomethyl group is attached to a quinoid system.

N-Benzylanilines are very readily converted to Schiff bases by the usual oxidizing agents, including chromic acid, potassium permanganate, iron chloride, etc. Hydrolysis of the schiff bases with acid yields the aldehydes.²⁶⁸ Oxidation is usually carried out in the temperature range 0 to 20° in aqueous solution using 10 to 20% excess of the oxidizing agent. Two-fifths of mole permanganate are required by theory per mole of benzyaniline.²⁶⁹

Ortho and *para* nitrobenzylanilines are converted to amino aldehydes by the action of sodium disulfide, the process evidently involving an internal oxidation.²⁷⁰

Other Methods Involving Direct or Indirect Oxidation of Methyl Groups

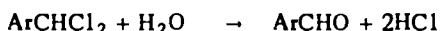
Homoanisaldehyde, $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{CHO}$, has been obtained in the form of its oxime on reducing anisylidenenitromethane, $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{CHNO}_2$.²³

Phenols and aromatic amines condense with formaldehyde in solution in a dilute acid or base to form substituted benzyl alcohols which may be oxidized directly to the corresponding aldehydes.²⁴ The aniline or phenol is mixed with an aqueous acid or alkali and the oxidizing agent, and reaction is allowed to proceed for several hours at the appropriate temperature. The mixture is then acidified and the aldehyde is isolated by steam distillation. Nitrosobenzene or phenylhydroxylamine may be used as the oxidizing agent; cupric oxide is employed as a catalyst. The formyl group enters the *para* position

preferentially, and yields are occasionally good, although they do not generally exceed 40 to 50% of theoretical. The method has been employed for the preparation of amino and hydroxy benzaldehydes on the technical scale.

Hydrolysis of Benzol Chlorides

Arylmethyl dichlorides may be readily hydrolyzed, as a rule, to aromatic aldehydes:



Hydrolysis proceeds well in many cases by simply boiling the dichloro compound with water.¹⁹ Hydrolysis is greatly accelerated by iron compounds; the presence of calcium carbonate also facilitates the reaction.

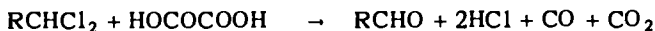
Hydrolysis may be effected by alkalies or with potassium acetate, the latter yielding the acetate of the corresponding aldehyde. Hydrolysis may be brought about also by heating with dilute or concentrated acids, depending on the type of halide. Concentrated sulfuric acid is often used for the purpose, especially on the industrial scale.

The process may be carried out as follows in the laboratory scale: The halide is mixed with three to four times its weight of 95% sulfuric acid, and the mixture is heated under vacuum at 50 to 70° while a stream of nitrogen or carbon dioxide is passed through the liquid, until the evolution of hydrogen chloride ceases. The time required for the completion of the reaction varies between three to twelve hours, depending on the type of halide. The aldehyde is isolated by pouring the reaction mixture on ice and removing the aldehyde which separates out as an oil layer. The final separation may be effected by steam distillation.²⁷¹

The effect of *ortho* substitution comes to evidence in acid hydrolysis, and dihalides with *ortho* substituents may be successfully hydrolyzed only at about 130°. ²⁷² Hydrolysis of 2,6-difluorobenzal bromide required heating with 10% oleum at 120° for eight hours. ²⁷³ Hydrolysis of pentachlorobenzal chloride also requires heating with oleum. ²⁷⁴

Conversion of difluoromethyl derivatives to the corresponding aldehyde may also be brought about by heating with concentrated sulfuric acid. ²⁷⁵

Aldehydes may be formed from benzal chlorides by heating with anhydrous oxalic acid at 110 to 130°. ²⁷⁶



The transformation may be brought about also by heating with boric acid for four hours. ²⁷⁷ Hydroxyl groups are not affected by these treatments, but trichloromethyl groups are converted to carboxyl groups.

Aldehydes from a Mixture of Calcium Salts

Aromatic aldehydes in which the aldehyde group is separated from the aromatic group by one or more carbon atoms may be prepared from the corresponding acids by heating the calcium salt of the latter with calcium formate:



Reduction of Acid Chlorides

Rosenmund Reduction

While in general aromatic acids cannot be reduced directly to aldehydes, conversion of aromatic acid chlorides to aldehydes can be readily accomplished by the Rosenmund method.²⁵ This consists in the partial reduction of the chloride in the presence of a catalyst consisting of 2 to 3% palladium supported on barium sulfate and containing a "regulator" or a catalyst poison. The regulators generally employed are "quinoline-sulfur", thioquinanthrene,²⁶ phenylisothiocyanate, and thiourea. An overdose of the regulator, or the presence of phosphorus compounds may inhibit the reaction. In many instances the use of a regulator may be dispensed with. The temperature at which the reduction is carried out has a great influence on the course of the reaction. Aldehydes are generally formed in optimum yield when the reduction is carried out at the lowest temperature at which an appreciable evolution of hydrogen chloride is observed.

Procedure

The reduction is generally carried out in xylene or toluene. A fifteen to thirty percent solution of the acid chloride is usually employed; the amount of catalyst added is 1/10 to 1/5 of the acid chloride present. About 10 grams of quinoline-sulfur regulator is used for every gram of catalyst. The reduction is carried out by bubbling hydrogen through the mixture heated to the appropriate temperature.

The apparatus employed for the reduction, as well as the solvent and catalyst, must be completely free of any traces of water, and the reaction mixture must be protected from atmospheric moisture. The liquid must be vigorously agitated during the operation.

The acid chloride is preferably prepared by use of thionyl chloride, rather than with phosphorus oxychloride. The acid chloride should be purified just prior to use, by distillation, or if a solid, by crystallization.

The aldehyde formed may undergo reduction to an alcohol; if this should occur, the alcohol formed reacts with an equivalent of the acid chloride to form an ester or the free acid; the latter reacts with the acid chloride to form the anhydride of the acid.

Some acid chlorides undergo reductive cleavage of the COCl group; this occurs during the reduction of many heterocyclic acid chlorides, and has also been observed in the preparation of *p*-anisoyl-3,4,5-trimethoxybenzoyl- and 2-naphthoylaldehydes. Triphenylacetyl chloride subjected to the Rosenmund reduction is quantitatively converted to triphenylmethane.

The yield of aldehyde in many cases is in excess of 50% and yields of 80% are not uncommon. The reaction is not generally applicable, however, and certain acid chlorides give a very low yield of aldehyde, or fail to give any aldehyde.

The method is applicable to the preparation of aliphatic as well as aromatic mono aldehydes; it has been employed for the preparation of many triterpene aldehydes.²⁷

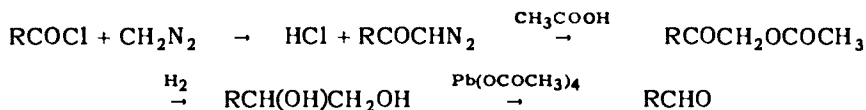
The chlorides of *dibasic acids* do not, as a rule, give dialdehydes; succinyl chloride, for example, gives principally butyrolactone, and *o*-phthalyl chloride gives phthalide. Dialdehydes are obtained, however, from *m*- and *p*-phthalyl chloride in excellent yield,²⁸ although 1,8-naphthalyl chloride fails to give a dialdehyde.

The carboxyl group in ortho hydroxy acids can be reduced to the formyl group with bisulfite in the presence of boric acid. Sufficient excess of bisulfite should be used for the formation of the bisulfite compound of the resulting aldehyde. The method has been used successfully for the preparation of aldehydes from salicylic acid, cresotic acid, 2-naphthol-2-carboxylic acid and some of their substitution products.²⁹ β -Naphthol-3-carboxylic acid gives tetrahydronaphthaldehyde in 25% yield.

Keto and nitro groups are not affected and even aliphatically bound halogens are not removed. The following aromatic and heterocyclic nitrated, halogenated, and keto aldehydes have been prepared by the Rosenmund reaction in the yield indicated: *p*-nitrobenzaldehyde, 91%; *o*-chlorobenzaldehyde, 70%; *m*-fluorobenzaldehyde, 60%; *m*- and *p*-trifluoromethylbenzaldehydes, 75 - 80%; *p*-acetylbenzaldehyde, 43%; 4-chloro-1-naphthaldehyde, 73%; 1-phenyl-3-chloro-5-methylpyrazole-4-aldehyde, 65%; 4,6-dichloropyridine-2-aldehyde, 50%; 2,6-dichloropyridine-4-aldehyde, 60%.

Saytzeff's method of reduction in the gas phase at about 200° over palladized asbestos is suitable for the preparation of aldehydes from the lower boiling acyl chlorides.²⁷⁸

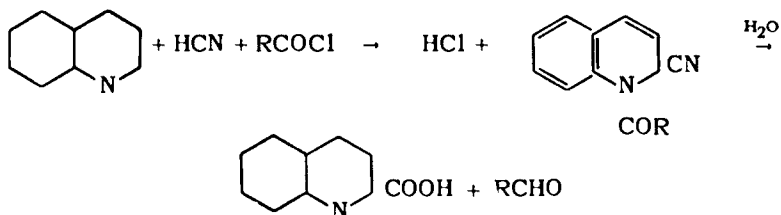
In *Grundmann's method*³⁰ the acid chloride is reduced indirectly to an aldehyde. The chloride is converted first to a diazoketone by reaction with diazomethane in an anhydrous medium; the diazoketone is converted to a keto ester by reaction with a carboxylic acid; this is then reduced to a glycol and the latter is oxidized with lead tetraacetate:



This reaction is applicable to aliphatic as well as aromatic acid chlorides.

Aldehydes from Reissert Compounds

Aldehydes are formed by the hydrolysis of Reissert compounds which result through the reaction of quinoline with hydrocyanic acid and an acyl chloride:²⁷⁹



The reaction is thus tantamount to an indirect reduction of acid chlorides.

The *procedure* in carrying out the reaction is as follows: Twenty to thirty cubic centimeters anhydrous hydrocyanic acid cooled to -5° are poured into a gram mole of freshly

distilled quinoline and a solution of half a gram mole of the acid chloride in 100 to 200 cc absolute benzene is added from a dropping funnel over a period of ten minutes with agitation and continued cooling. The reaction is generally complete at room temperature within about sixteen hours.

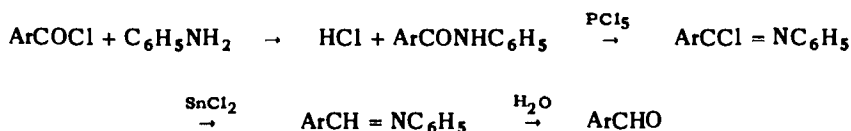
The Reissert compound is taken up in 1000 to 2000 cc ether, the solution is repeatedly washed with 100 cc portions of water, then with saturated aqueous sodium carbonate solution, and finally with water again. The ether is next evaporated off and the nitrile is hydrolyzed by boiling with 1500 cc of 5 - 10 *N* sulfuric acid. The aldehyde may be isolated by extraction, steam distillation or, if it is a solid, simply by filtration. The aldehyde may be distilled over with steam during the hydrolysis of the Reissert compound.

The reaction has been extended to aliphatic acyl halides since the discovery that Reissert compounds may be prepared from aliphatic acid chlorides by carrying out the reaction with quinoline and hydrocyanic acid in non-aqueous media.²⁸⁰

Isoquinoline and phenanthrene may serve instead of quinoline in the preparation of Reissert compounds.²⁸¹

Sonn-Müller Reaction³²

This reaction also constitutes an indirect method of reduction of acyl chlorides to aldehydes. The chloride is converted to the anilide by reaction with aniline, the anilide is changed to a chloroimide by reaction with phosphorus pentachloride, the chloroimide is reduced with stannous chloride to an aldimine, and the latter is hydrolyzed to the aldehyde:



The *procedure* is as follows: The anilide is converted to the chloroimide by treatment with an equimolecular quantity of phosphorus pentachloride in solution in an anhydrous hydrocarbon or chlorinated hydrocarbon. The crude imidochloride remaining after the removal of the solvent and the phosphorus oxychloride by distillation under vacuum is added to three to four molecular equivalents of stannous chloride previously treated with an ethereal solution of hydrogen chloride. The imido chloride may be placed in solution in an inert solvent before it is mixed with the stannous chloride. Reduction is generally complete in two to twelve hours. The tin salt complex, or the entire reaction mixture, is next heated with dilute hydrochloric acid and the aldehyde formed isolated by an appropriate procedure.

Thionyl chloride may be substituted effectively for phosphorus pentachloride in the preparation of aromatic imidochlorides.

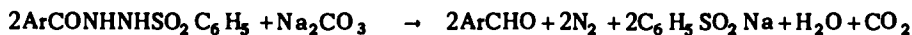
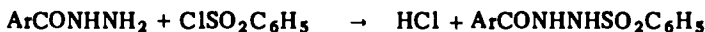
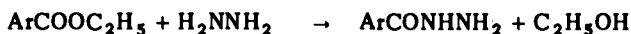
The reaction is generally applicable to aromatic amines which do not contain substituents affected by phosphorus pentachloride or stannous chloride. It is not applicable, however, to simple aliphatic amides, since aliphatic imidochlorides are unstable and undergo spontaneous decomposition.²⁸² α,β -Unsaturated imidochlorides are more stable and aldehydes have been prepared from a number of such chloroimides in good or moderate yield.²⁸³ The Sonn-Müller reaction has

been employed successfully for the preparation of aldehydes from 1-, 2-, 3- and 9-phenanthrenecarboxylic acids; yields of aldehydes are somewhat low, however.

Attempts to extend the reaction to heterocyclic amides have only been partially successful.²⁸⁴

McFayden-Stevens Reaction³³

This reaction involves the conversion of an ester successively to a hydrazide and benzenesulfonyl hydrazide, and decomposition of the latter with sodium carbonate:

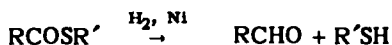


The acyl sulfonyl hydrazides are prepared by adding the aryl sulfonyl chloride in small portions to the cooled solution of the hydrazide in dry pyridine. The mixture is allowed to stand at room temperature and is then poured into a small excess of ice-cold dilute hydrochloric acid. The precipitated acyl sulfonyl hydrazide is recrystallized from a suitable solvent. Decomposition of the benzene-sulfonyl hydrazide is accomplished by heating the compound at 160° with four to six equivalents of anhydrous sodium carbonate suspended in ethylene glycol.

The method is applicable exclusively to aromatic bodies, and gives variable results, yields ranging 40 to 85%; it fails when applied to compounds in which the carbonyl group is not directly attached to a ring system. The reaction has been used successfully for the preparation of aldehydes of the thiazole, pyrimidine, pyridine and quinoline series.³⁴

Hydrogenolysis of Thiol Esters

Hydrogenolysis of thiol esters gives aldehydes if the reduction is carried out by use of partially deactivated nickel as catalyst.³¹

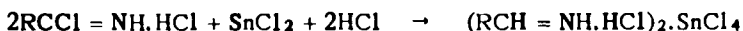
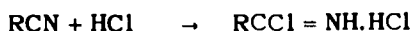


The catalyst is deactivated by heating it under reflux in suspension in acetone. Simple aromatic aldehydes have been prepared by this method.

Thiol esters are readily obtained through the reaction of thiols with acid chlorides in pyridine solution.

Stephen's Synthesis³⁵

Stephen's aldehyde synthesis consists in the transformation of the chlorimine formed by the reaction of a nitrile with hydrogen chloride into an aldimine by reduction with stannous chloride. The aldimine hydrochloride is obtained in the form of a complex with stannous chloride.



Hydrolysis of the aldimine complex gives the aldehyde.

The procedure is as follows: Hydrogen chloride is passed through a suspension of one and a half to six molal equivalents of anhydrous stannous chloride in anhydrous ether until two layers appear, the operation generally requiring several hours. One molecular equivalent of the nitrile is then added with good stirring, and the mixture is allowed to stand until the precipitation of the crystalline aldimine hydrochloride-stannic chloride complex is complete. This may require two to twenty-four hours. The complex is then filtered and hydrolyzed by boiling with water. The aldehyde formed may be isolated by steam distillation or by extraction with ether.

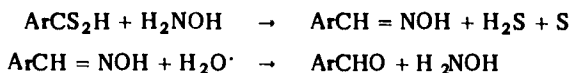
A little chloroform may be added to the ether used for the preparation of the aldimine chloride in order to enhance the solvent power of the liquid for the nitrile. If the nitrile is insoluble in ether, it is dissolved in chloroform and the solution is added to the mixture of ether and the reducing agent. With some nitriles cooling of the ether-stannous chloride-hydrogen chloride-nitrile mixture after some hours, and its resaturation with hydrogen chloride may be necessary. High yields of aldehydes have been obtained with stannous chloride containing 1.4 to 1.5% moisture.²⁸⁵

The stannous chloride may be prepared by gradually adding with agitation 1 gm mole of stannous chloride dihydrate to 2.06 gm moles of acetic anhydride. The mass is allowed to cool to room temperature, the supernatant liquid is poured off, the chloride is washed with ether by decantation, and is filtered. The compound may be kept indefinitely when protected from atmospheric moisture.²⁸⁶

The reaction is applicable to aliphatic as well as aromatic nitriles. While excellent yields are obtained in many cases, the results are not uniformly good. Benzaldehyde and naphthaldehyde have been obtained in yields in excess of 90%, but negligible amounts of aldehydes are obtained in many instances, and the reaction fails completely, for example, when applied to 4-cyanodiphenyl. Steric factors are operative in many cases of reported failure. Nitro groups do not interfere in the reaction, but may undergo reduction if a sufficient excess of stannous chloride is used. Only a few heterocyclic nitriles have been successfully converted to aldehydes by this method.²⁸⁷

Conversion of Dithiocarboxylic Acids to Aldehydes

Aromatic dithioacids can be converted to aldehydes by reaction with hydroxylamine, semicarbazide, or *as*-phenylmethylhydrazine, followed by hydrolysis of the resulting product:³⁶

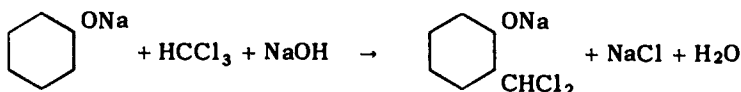


Nuclear Syntheses

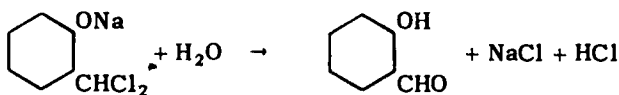
Outstanding among the methods directed at the introduction of the aldehyde group into the aromatic nucleus are those of Reimer and Tiemann, of Gatterman and Koch, and of Gattermann.

Reimer-Tiemann Synthesis³⁷

This method is based on the reaction of chloroform with an alkali phenolate in the presence of excess caustic:



Hydrolysis of the dichloro compound formed with acid results in the formation of a phenolic aldehyde:



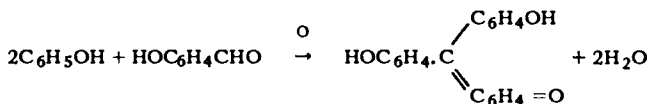
The aldehyde group enters the *ortho* or *para* position with respect to the hydroxy group.

Procedure

Dilute aqueous solutions of sodium hydroxide and the sodium compound of the phenol are heated at 50 to 70° and the chloroform is added gradually, finally heating the mixture under reflux for several hours. The chloroform and alkali are used in large excess, about two or three times the amount calculated on the basis of the ketone used. After cooling, the reddish-violet reaction mixture is made strongly acid, and the precipitated phenol is removed. The *ortho* hydroxy aldehyde is then separated from the less volatile *para* hydroxy compound by steam distillation.

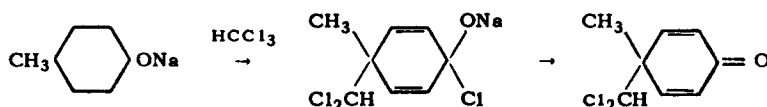
If the alkali phenolate is only slightly soluble in water, it may be brought into solution by adding pyridine. Aqueous pyridine may be used in place of aqueous caustic; only the *ortho* isomer is obtained when this modification is introduced. Yields are improved when some alcohol is added to the chloroform. Bromoform, iodoform, or trichloroacetic acid may be used in place of chloroform; chloral has also been used in the reaction with success.

The reaction proceeds successfully with most phenols containing an available activated position, and offers a useful means for the preparation of phenolic aldehydes, but it does not appear to be applicable to hydrocarbons, phenol ethers, and tertiary amines. The quantity of the *ortho* isomer formed usually exceeds that of the *para* isomer. Salicylaldehyde is obtained, for example, in 37 to 45% yield, with 8 to 11% of the *para* isomer. Up to 20% of the phenol may react to form an *ortho* ester. A considerable proportion of the aldehyde formed from phenol condenses with unreacted phenol to give aurin:



Some resinous product is also formed, which contains complex products of the triphenylmethane series, such as rosolic acid. Occasionally traces of dialdehyde are also formed, yields seldom exceed 50% of the theoretical, and are less than 25% when the ring contains electronegative groups, such as sulfo, cyano, carboxyl, and nitro groups. *o*-Nitro-*o*-bromophenol reacts more readily than the *para* compounds. 2-Hydroxy-1-naphthaldehyde is obtained from β -naphthol in exceptionally good yield.

When *p*-hydroxy carboxylic acids are used in the reaction, the carboxyl group may be eliminated and replaced by the aldehyde group, *p*-hydroxybenzoic acid giving, for example, *p*-hydroxybenzaldehyde as well as a carboxylic hydroxyaldehyde. Chlorinated derivatives of ketodihydrobenzene are obtained from *ortho* and *para* alkylated phenols in addition to the aldehyde:³⁸



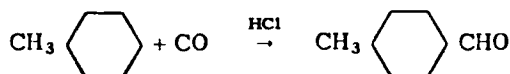
Pseudocuminol gives a considerable proportion of 2,4,5-trimethyl-4-dichloromethyl-1,5-cyclohexadienone-1, together with 5% of aldehyde. *p*-Cresol gives 35% of homosalicinaldehyde and 12% of chloromethylated products; *p*-cresol gives only about half as much of the ketonic product under optimum conditions.

The dichloromethyl product may be isolated by acidifying the reaction mixture, steam distilling the product to effect a partial separation from resinous materials, extracting the distillate with alkali, and recovering the dichloro compound by fractional crystallization.

The reaction has been extended to heterocyclic compounds. The 3-aldehyde compound has been obtained, for example, from indole and 2-methylindole;³⁹ the 5-aldehyde has been obtained from 6-hydroxyquinoline, and the 8-aldehyde from the 7-hydroxy compound.⁴⁰ Quinaldine-3-aldehyde has been prepared from 4-hydroxyquinaldine, and tetramethyl-4-quinoline-3-aldehyde from 4-hydroxy-2,5,6,8-tetramethylquinoline.⁴¹

The Gattermann-Koch Synthesis⁴²

In this method carbon monoxide and hydrogen chloride are made to react with an aromatic hydrocarbon in the presence of a mixed catalyst consisting of cuprous chloride and aluminum chloride, to form an aldehyde:



It may be assumed that formyl chloride is formed in the reaction as a transient intermediate. The function of cuprous chloride is apparently that of binding carbon monoxide in the form of an unstable molecular complex.

The *procedure* is to conduct a stream of hydrogen chloride for several hours through a solution of the aromatic compound in anhydrous ether or in nitrobenzene containing the mixture of cuprous chloride and aluminum chloride in suspension. The carbon monoxide should pass through the liquid twice as fast as the hydrogen chloride. Usually a molecular equivalent of aluminum chloride is employed for each mole of hydrocarbon to be formylated. The solution is maintained at 25 to 35°, although in certain instances a temperature of 50 to 60° has been found more advantageous. The reaction requires from 4 to 8 hours for completion. Toward the end, the reaction the mixture thickens and stirring becomes difficult. After completion of the reaction, ice is added to the mixture, and the aldehyde is recovered in the usual manner. The yields are generally low.

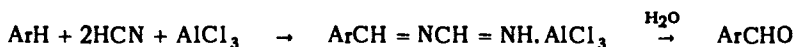
The industrial grade of aluminum chloride may be used in the reaction. Exposure of the chloride to atmospheric moisture is said to improve its activity. The cuprous chloride may be replaced by titanium chloride or nickelous chloride. Benzene may be used as a solvent. Resinous products are formed in appreciable amounts if the time of reaction is unduly prolonged, especially if the reaction is carried out at the higher temperature. Iron pentacarbonyl, $\text{Fe}(\text{CO})_5$, may be used for the formylation of aromatic compounds in the absence of a catalyst.⁴³ In some modifications of the reaction, formyl-substituted secondary amines, or formamide and ammonium chloride are used.⁴⁴

Benzene does not react under the normal conditions of the reaction, but this hydrocarbon may be formylated by use of aluminum bromide as a catalyst.¹²⁵ Reaction may be effected also under pressure, especially when small amounts of titanium chloride or copper chloride are added to the catalyst.¹⁹⁹ Toluene gives a fair yield of *p*-tolualdehyde; ethylbenzene gives a low yield of aldehyde and considerable amounts of high boiling condensates.⁴⁵ An alkyl group in the aromatic nucleus directs the formyl group to the *para* position.⁴⁶ Formylation of isopropylbenzene is accompanied by side reactions; 2,4-diisopropylbenzaldehyde and a little benzaldehyde are formed in addition to the main product. If two alkyl groups occupy *para* positions in the nucleus, removal of one and its replacement by the aldehyde group may occur.⁴⁷ Alkylation of the nucleus by alkyl exchange has also been observed. Alkylation and dealkylation are apt to take place when the reaction is applied to the more highly alkylated aromatic compounds. A migration of the alkyl group within the molecule has also been observed.⁴⁸ The reaction is not applicable to phenols or their alkyl ethers, and to nitro compounds. Chlorobenzene has been formylated in nitrobenzene solution under atmospheric pressure. Biphenyl has been converted to *p*-phenylbenzaldehyde,⁴⁹ and hydrindene has been converted to the 5-aldehyde, while diisopropyl-*α*-tetrahydronaphthalene gives diisopropyl-*α*-tetrahydrophthalaldehyde. Naphthalene fails to give an aldehyde by this reaction.

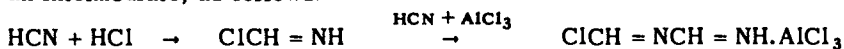
Aromatic hydrocarbons which fail to undergo the Gattermann-Koch reaction under atmospheric pressure may react with carbon monoxide under high pressure.⁵⁰ Benzene, for example, may be converted to benzaldehyde in good yield by reaction with carbon monoxide under a pressure in excess of 300 lb/sq in.

Gattermann Synthesis⁵¹

Hydrocyanic acid combines with aromatic compounds in the presence of hydrogen chloride and aluminum chloride to form an arylmethyleneformamidine complex, hydrolysis of which results in the formation of an aromatic aldehyde:



A chloromethyleneformamidine-aluminum chloride complex is apparently formed as an intermediate, as follows:



and reacts with the aromatic compound to form the arylmethyleneformamidine complex.

Procedure

The reaction may be carried out in an inert solvent or an excess of the aromatic compound, if the latter is a liquid at room temperature. When the reaction is carried out in a solvent, powdered aluminum chloride and the solvent are mixed, the required quantity of hydrocyanic acid is added, and the mixture is kept at room temperature for fifteen minutes. The aromatic compound is then added, while simultaneously, a slow current of hydrogen chloride is conducted through the mixture for fifteen minutes. The mass is then heated on a water bath with occasional agitation while the passage of hydrogen chloride is continued. The resulting dark, viscous product is poured into a mixture of ice and

concentrated hydrochloric acid, and the whole is heated to boiling for fifteen minutes. The aldehyde formed is isolated by the usual methods.

It is important that a quantity of aluminum chloride in excess of that required for the formation of the hydrocyanic acid-aluminum chloride complex, $2\text{HCl} \cdot \text{AlCl}_3$, be used. The yield of aldehyde improves with increase in the excess of aluminum chloride used, up to a maximum value corresponding to the optimum amount of the chloride. The solvent employed has a marked effect on the course of the reaction. *p*-Methoxybenzaldehyde may be obtained from anisole in yields ranging up to 50% when the reaction is carried out in the absence of a solvent or in ethylbenzene, but the reaction fails to proceed in carbon disulfide, nitrobenzene, and certain other solvents.

The reaction may be carried out by use of sodium cyanide or zinc cyanide;⁵² the latter acts as a catalyst in the presence of a small amount of sodium chloride.

Chlorobenzene, *o*-dichlorobenzene, and tetrachloroethane are satisfactory solvents. It may often be of advantage to carry out the reaction in the temperature range 60-100°.

The yield of aldehydes from aromatic hydrocarbons by this method, following the best procedure, is generally low; benzaldehyde is obtained in 11 to 39% yield from benzene, and *p*-ethylbenzaldehyde in 22 to 27% yield from ethylbenzene. 9-Anthraldehyde and mesityl aldehyde are obtained in good yields from the corresponding hydrocarbons.

In contrast with the Gattermann-Koch synthesis, the Gattermann reaction is applicable to phenols and phenol ethers. Dihydric phenols with hydroxyl groups in meta position to one another are so reactive that condensation can be carried out in the presence of zinc chloride as a catalyst.⁵³ Pyrocatechol and hydroquinone react poorly. Mono- and dihydroxynaphthalenes can be condensed with hydrocyanic acid by use of zinc chloride as a catalyst.⁵⁴ Phloroglucinol reacts very readily with hydrocyanic acid and hydrogen chloride even in the absence of a catalyst. The other trihydric phenols also undergo the reaction readily.

Hydroxyl and alkoxy groups exert a para directing influence. The directive influence of allyl, ethyl, *n*-propyl, benzyl, and methoxy groups increases in the order named. If the para position is already occupied, then the methyleneformamidine group enters the ortho position. β -Naphthol readily yields an *ortho* aldehyde. In general, phenol ethers give better yields of aldehyde, although the reaction proceeds somewhat less readily with ethers than the free phenols.

Substituents in the aromatic ring other than chlorine, hydroxyl, or alkoxy groups retard or completely inhibit the reaction. The nitro, carboxyl, amino, azo, acetyl groups and quinoid oxygen exert a particularly strong inhibitive influence. 2-Hydroxy-, 2-methoxy-, and 2,2'-dihydroxydiphenyl do not undergo the Gattermann reaction.

Gattermann's synthesis has been successfully applied to 3-phenanthrol,⁵⁵ furans,⁵⁶ coumarones,⁵⁷ dibenzofuran,⁵⁸ pyrroles,⁵⁹ 3-methylindole,⁶⁰ and indole-2-carboxylic esters.⁶¹ Pyrrole reacts more readily than furan, and the latter reacts more readily than thiophene; all three yield 2-carbonyl derivatives.⁶² Diphenyl oxide gives a 4-carbonyl derivative.⁶³

Aldehydes result through the reaction of polyhydric phenols with mercury fulminate and hydrochloric acid, and hydrolysis of the oxime formed:⁴⁴



Vilsmeier and Haack's Method

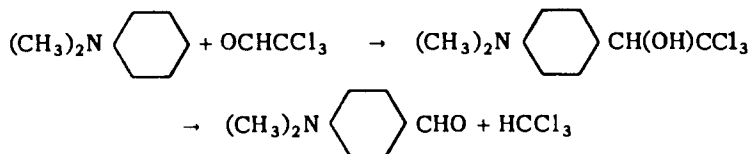
Aldehydes are obtained in the form of their phenylimines by the action of formanilide and phosphorus oxychloride on polyhydric phenols.⁶⁴ Vilsmeier and Haack⁶⁵ employed N-methylformanilide in place of formanilide and obtained satisfactory results. The reaction was carried out by allowing the aromatic compound, N-methylformanilide, and phosphorus oxychloride to react at the appropriate temperature, then an aqueous solution of sodium acetate was added and the mixture was steam distilled to liberate the aldehyde. N,N-Dialkylamino and alkoxy derivatives of aromatic compounds were formylated readily by this method, as were also naphthols and certain hydrocarbons containing a reactive hydrogen. Yields averaged 70 to 85%.

Other Methods of Introduction of the Aldehyde Group into the Nucleus

Aldehydes have been prepared also through the reaction of anhydroformaldehydeaniline, $(\text{CH}_2\text{NC}_6\text{H}_5)_3$, with phenol ethers, subsequent dehydrogenation of the benzyanilines formed with nitrobenzene and potassium hydroxide, and hydrolysis of the resulting phenylimine.⁶⁶

In *Duff's method* the aldehyde group is introduced into the nucleus of the phenols and anilines by reaction with hexamethylenetetramine in the presence of glycerine borate or ethoxyethanol borate. The reaction mixture is heated for a short time at 150 to 170° and is then rapidly chilled.²⁸⁸ The reaction appears to involve the formation of a secondary amine, e.g., $\text{HOArCH}_2\text{NHCH}_2\text{ArOH}$, followed by a Sommelet reaction. The formyl group enters the *ortho* position to the hydroxyl group in phenols, and the *para* position in dialkylanilines. The method has been used extensively in the preparation of aldehydes from flavones.²⁸⁹ The reaction has been applied successfully to thiophene and thiophene derivatives.²⁹⁰

*Böessneck's method*⁶⁷ consists in reacting tertiary aromatic amines with chloral hydrate in the presence of zinc chloride at a moderate temperature, and decomposing the resulting hydroxy compound by boiling with caustic solution:



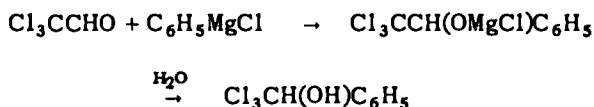
The method has been successfully extended to the preparation of a number of other aldehydes, including vanillin,³⁰⁵ syringaaldehyde,³⁰⁶ and antipyrine aldehydes.³⁰⁷

Trichloromethylcarbinols are not formed with equal ease. Thus, while condensation between chloral and bis-1,3-dimethylaminobenzene proceeds below 15°, that between 1-hydroxy-2-ethoxybenzene and chloral proceed at room temperature, while the condensation of antipyrine and chloral is effected at 120°.

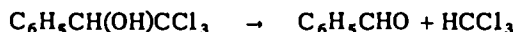
Conditions under which cleavage of trichloromethyl carbinols is brought about also vary widely. The trichloromethylcarbinol derived from bis-1,3-dimethylaminobenzene is cleaved by heating to 90° for fifteen minutes with 30% caustic; the trichloromethylcarbinol from 1-hydroxy-1-ethoxybenzene is treated with alcoholic caustic at 30° for six

hours, while the carbinol from antipyrine is heated at 120° for two hours with aqueous potassium carbonate. The latter treatment is employed when the aldehyde is sensitive to caustic.

Chloral condensation products of aromatic compounds may be prepared through the interaction of aromatic halomagnesium derivatives with chloral:⁶⁸

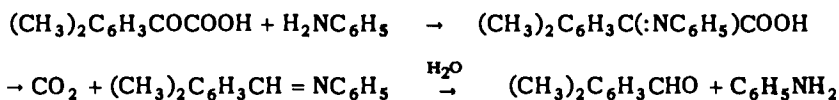


These compounds also give aldehydes on boiling with potassium carbonate:

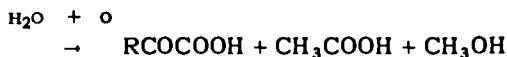
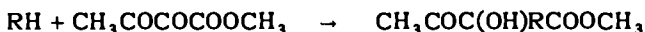


Better yields are obtained by this treatment than on heating with caustic, since the latter tends to destroy the aldehyde.

Arylglyoxylic acids, RCOCOOH , which are readily obtainable by synthetic methods, give benzlidene anilines, $\text{RCH} = \text{NHC}_6\text{H}_5$, when heated with aniline; these are readily converted to an aldehyde and aniline by hydrolysis with dilute acids:⁶⁹



Tertiary anilines, phenols, and aromatic hydrocarbons may be made to condense with α,β -diketo carboxylic esters, and with mesoxalic esters, to form acyl-arylglycollic esters and aryltartronic esters. These may be converted into arylglyoxylic acids by oxidation with cupric acetate, or by heating with concentrated sulfuric acid:⁷⁰



The glyoxylic acids obtained can then be transformed to aldehydes as above.

Aryl magnesium halides react with alkoxyacetals of the type $\text{ROCH}_2\text{CH(OR)}_2$ to form a mixture of arylated ethers and vinyl ethers:



When treated with dilute sulfuric acid, both of these products are converted first into an unstable arylvinyl alcohol, and then into an aldehyde:



Aromatic Aldehydes with other Functional Groups

Primary *aldehyde alcohols* are obtained by the action of formaldehyde and caustic potash on alkylated aromatic aldehydes.⁷¹ Phenolic aldehyde alcohols

may be prepared by the action of formaldehyde and hydrochloric acid on phenol aldehydes.⁷²

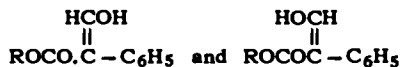
Formylphenylacetic acid, $\text{C}_6\text{H}_5\text{CH}(\text{CHO})\text{COOH}$, and its analogs have been obtained in the form of their esters through the condensation of the ester of phenylacetic acid with formic ester in the presence of sodium:⁷³



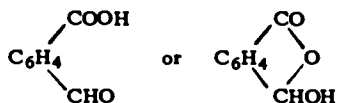
Formylphenylacetic acid and other similar compounds are tautomeric bodies and exist in the *aldo* and *enol* forms:



The enol form is known in two isomeric modifications:



Substituted *ortho* aldehydic acids have been prepared from naphthalene derivatives.⁷⁴ Such compounds can be formulated as lactones or pseudo derivatives as well as aldehyde acids



Derivatives of both types of compounds are known.

Nitration of benzaldehyde with a mixture of sulfuric and nitric acids leads largely to the formation of *m*-nitrobenzaldehyde,⁷⁵ and the compound may be readily prepared in the pure form by this method.

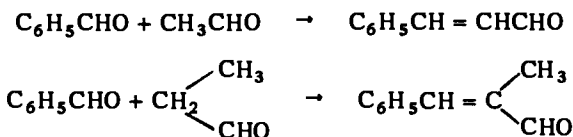
o-Nitrobenzaldehyde may be prepared through the oxidation of *o*-nitrocinnamic acid, $\text{NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHCOOH}$, with potassium permanganate. *p*-Nitrobenzaldehyde has been obtained from *p*-nitrobenzyl chloride by boiling with lead nitrate solution; the compound has also been made by the oxidation of *p*-nitrotoluene with chromyl chloride, and most readily through the oxidation of *p*-nitrocinnamic acid. *2,4-Dinitrobenzaldehyde* is obtained by the oxidation of *2,4*-dinitrobenzyl aniline, or its sulfonic derivative, with potassium permanganate or chromic acid. Schiff's bases are first formed and are then decomposed by acid.

Ortho and *para* aminobenzaldehydes are prepared through the reduction of the corresponding nitrobenzaldoximes with ammonium sulfide and subjecting the resulting oximes to the action of ferric chloride.⁷⁶ *o*-Aminobenzaldehyde may be prepared also through the reduction of *o*-nitrobenzaldehyde, or anthranil, with ferrous sulfate and ammonia.⁷⁷ *m*-Aminobenzaldehyde is obtained from *m*-nitrobenzaldehyde by reduction with tin and acetic acid. *p*-Aminobenzaldehyde is prepared through the molecular rearrangement of *p*-nitrotoluene.⁷⁸ The freshly prepared crystalline *p*-aminobenzaldehyde is water-soluble, but it rapidly changes to an amorphous, insoluble product. Aromatic amino aldehydes are obtained further by condensing halo aldehydes with arylsulfonamides in the presence of agents capable of combining with acids. The *N*-aryl sulfonaminoaldehydes, $\text{OHC}_6\text{H}_4\text{NHSO}_2\text{C}_6\text{H}_5$, which are formed are hydrolyzed to amino aldehydes.⁷⁹

Halogenated benzaldehydes are prepared from halogenated benzylidene chloride by the action of oxalic or sulfuric acid,⁸⁰ or by oxidizing halogenated cinnamic acids.

Benzaldehyde-o-sulfonic acid is obtained by the action of sodium sulfite on ortho-chlorobenzaldehyde, and by oxidizing o,o-stilbenedisulfonic acid. The chloride of this acid, treated with ammonia and subsequently oxidized by atmospheric oxygen, is converted to saccharin.⁸¹

α,β -Unsaturated aldehydes may be prepared through the condensation of aromatic aldehydes with aliphatic aldehydes in dilute caustic solution:⁸²



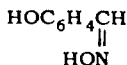
Behavior and Reactions of Aromatic Aldehydes

The characteristic reactions of aldehydes are shown by aromatic aldehydes. They combine with hydroxylamine and hydrazine to form oximes and hydrazones. They yield addition compounds with sodium acid sulfite, and cyanohydrins are obtained by reaction with hydrocyanic acid. Aromatic aldehydes react with primary amines, forming Schiff bases. They undergo the Cannizzaro reaction and the acyloin condensation, and are capable of condensing with compounds containing a reactive methyl or methylene group.

Reaction with Hydroxylamine, Hydrazines, etc.

Aromatic oximes are obtained by the same methods as those employed for the preparation of aliphatic oximes. They may be obtained through the direct reaction of the aldehyde and the free oximes; for example, benzaldoxime results by the reaction of benzaldehyde and hydroxylamine.

As a general rule, aromatic aldehydes in which the formyl group is joined directly to the aromatic nucleus give both stereoisomeric oximes, although benzaldehyde yields only the *anti* compound. The presence of a hydroxyl group in the ortho position to the formyl group causes the formation of only one stereoisomeric form of the oximes, the *anti* compound.⁸³



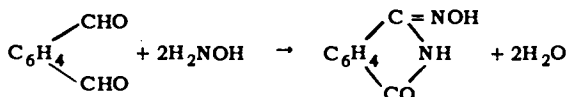
Alkoxy groups in the *ortho* position do not prevent the formation of the two stereoisomeres. Oximes of aromatic aldehydes with an aliphatically bound aldehyde group have been obtained largely in one modification, probably the *syn*-isomer.⁸⁴

The *syn* isomer of aldoximes is more stable toward alkalies and labile toward dilute acids; for this reason the hydrochlorides of both isomeric oximes give principally the *anti* oxime when decomposed with water, and the *syn* oxime when decomposed with sodium hydroxide solution. An exception is presented by *ortho* substituted aldoximes, such as o-chlorobenzaldoxime, both stereoisomers of which are stable toward alkalies.⁸⁵

Benzaldehyde *anti* oxime may be converted to the *syn* isomer by treating it in ethereal

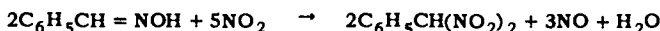
solution with hydrogen chloride at room temperature and decomposing the resulting hydrochloride with aqueous sodium hydroxide.⁸⁶ The *syn* isomer may, in turn, be converted to the *anti* oxime by boiling its ethereal solution for some time. The sodium salt of the *anti* oxime is electrolytically dissociated, while the sodium *syn* oxime is hydrolyzed with water to the free *syn* oxime and sodium hydroxide. This behavior is typical of isomeric aldoximes. The β -oxime can usually be transformed into the isomeric α -oxime with great ease. The reverse change can be effected via the hydrochlorides, of which the β -isomer is more stable than the α -form.

The reaction of hydroxylamine with o-phthalaldehyde results in the formation of phthalimidoxime



Benzaldehyde *anti* oxime reacts with sodium bisulfite to form a crystalline compound, $\text{C}_6\text{H}_5\text{CH}(\text{SO}_3\text{Na})\text{NHSO}_3\text{Na} \cdot 3\text{H}_2\text{O}$, which is decomposed by dilute acids to benzaldehyde, sodium sulfate, sulfurous acid, and ammonia.

Benzaldoxime reacts with nitrogen dioxide to form phenyldinitroethane in 38% yield, in accordance with the equation:⁸⁷

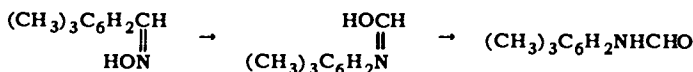


This is known as the *Pinzio reaction*.

Both isomers of benzaldoxime react with benzyl chloride in cold alcoholic alkaline solution, the *anti* isomer giving N-benzylbenzaldoxime, $\text{C}_6\text{H}_5\text{CH}(\text{NCH}_2\text{C}_6\text{H}_5)$. Sub-

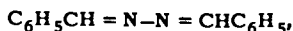
jected to the action of chlorine in well-cooled chloroform solution, both isomeric forms of benzaldoxime give benzhydroximic chloride, $\text{C}_6\text{H}_5\text{CCl}=\text{NOH}$.

The more stable *anti* aldoximes undergo the Beckmann's transformation under the influence of phosphorus pentachloride to yield an amide:⁸⁸



The less stable aldoximes, which are readily converted to the *syn* isomer, give nitriles when treated with the same reagent.

Benzalhydrazine, $\text{C}_6\text{H}_5\text{CH}=\text{NNH}_2$, is formed when benzaldehyde is added slowly to about half its weight of hydrazine hydrate, $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, containing a few pieces of barium oxide. The compound rapidly changes to benzalazine,

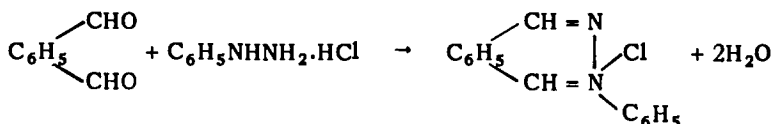


in contact with moist air or acids; the same transformation can be effected by treatment with an ethereal solution of iodine. Benzalazine is obtained very readily through the interaction of benzaldehyde and hydrazine. It is decomposed to benzaldehyde and hydrazine sulfate when boiled with 20% sulfuric acid.

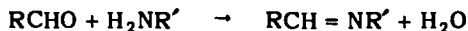
Phenylhydrazine reacting with aromatic aldehydes gives hydrazones,



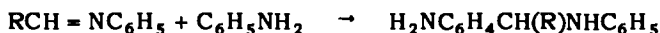
The hydrochloride of hydrazine reacting with o-phthalaldehyde gives phenylphthalazonium chloride:



The reaction of primary aromatic amines with aromatic aldehydes proceeds quite readily, giving aromatic anils:⁸⁹

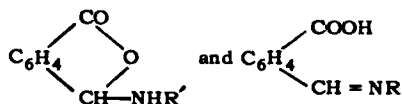


It is usually sufficient to mix the amine and aldehyde in alcoholic solution and to warm the mixture gently. The compounds crystallize well and may serve for the purpose of identifying aromatic aldehydes. Anils decompose into their component aldehyde and amine when heated with dilute aqueous acids. Anils react additively with aromatic amines:



Benzaldehyde reacts with ammonia in concentrated aqueous solution to form a hydrobenzamide, $\text{C}_6\text{H}_5\text{C} = \text{NCH}(\text{C}_6\text{H}_5)\text{N} = \text{CHC}_6\text{H}_5$. Other aromatic aldehydes behave similarly.⁹⁰ The reaction of benzaldehyde with aniline hydrochloride in aqueous solution gives the hydrochloride of the addition compound, $\text{C}_6\text{H}_5\text{NHCH}(\text{OH})\text{C}_6\text{H}_5$. Addition compounds of this type are also obtained with certain nitrobenzaldehydes.⁹¹

Phthalic acid aldehyde reacts readily with amines even at atmospheric temperature to form two series of compounds:⁹²



Compounds of the first series are insoluble in aqueous alkalis, while those of the second series readily dissolve in caustic solution. Opiatic acid gives similar compounds by reaction with amines.

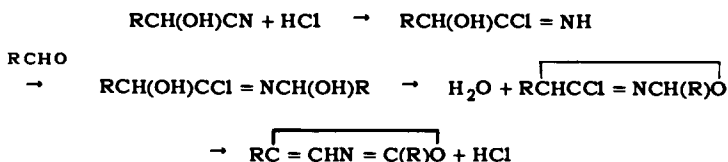
Addition Reactions

Benzaldehyde cyanohydrin and cyanohydrins of other aromatic aldehydes may be prepared through the reaction of the aldehydes with nascent hydrocyanic acid generated by adding sulfuric acid to a solution of an alkali cyanide.⁹³ Salicylaldehyde cyanohydrin and many other aromatic cyanohydrins have been prepared through the direct interaction of the aldehyde with hydrocyanic acid in the presence of a small amount of alkali metal cyanide.⁹⁴

Benzaldehyde cyanohydrin and substituted benzaldehyde cyanohydrins have been prepared from the bisulfite compound of the aldehyde by reaction with an alkali metal cyanide.⁹⁵

A satisfactory procedure is to dissolve the aldehyde in the solution of bisulfite heated to 50° , and to add concentrated aqueous potassium cyanide dropwise and with good agitation, to the resulting mixture cooled to 0° . The cyanohydrin formed may be isolated by extraction with ether. The compound may be obtained in a partially purified form by washing the extract with aqueous sodium bisulfite and water, drying with calcium chloride, and evaporating off the ether.

Oxazoles result through the interaction of benzaldehyde and substituted benzaldehydes and cyanohydrins in the presence of hydrogen chloride:⁹⁶



Mandelonitrile condenses with phenols at 100° in the presence of 73% sulfuric acid to form phenylhydroxyphenylacetonitriles:⁹⁷



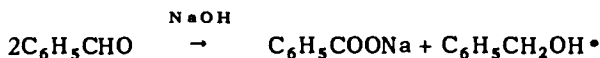
Condensation also takes place with substituted mandelonitriles and the yields are generally good.

Aromatic aldehydes, as a rule, react readily with *sodium bisulfite* to form addition compounds.⁹⁸ Aldehydes related to thymol and carvacrol form an exception.⁹⁹

Addition compounds have been obtained through the reaction of aromatic aldehydes with aromatic acyl chlorides and with oxalyl chloride.¹⁰⁰ These have the structure $\text{RCH(Cl)OCOR}'$.

Cannizzaro Reaction

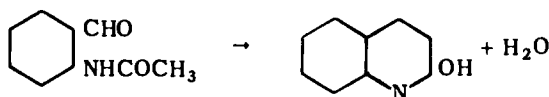
Benzaldehyde and mono- and polysubstituted benzaldehydes in which two substituents are not in the *ortho* position, smoothly undergo the Cannizzaro reaction:¹⁰¹



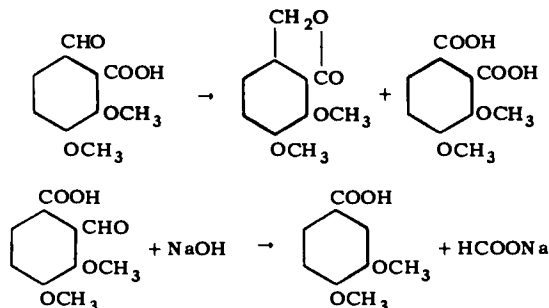
The reaction is carried out by mixing the aldehyde with an excess of 50% sodium hydroxide. The mixture is well agitated while the temperature is maintained at about 45°, by cooling if necessary. Nitrobenzaldehydes undergo the reaction very readily, with evolution of considerable heat, and it is necessary to use caustic of 15 to 35% concentration in order to make possible proper control of temperature.

When both *ortho* positions in the aldehyde are occupied with a halogen or a nitro group, the Cannizzaro reaction does not take place, and the formyl group is replaced with hydrogen. 2,4-Dinitrobenzaldehyde also undergoes this reaction, but 2-nitro-4-halo- and 2-halo-4-nitrobenzaldehyde undergo the normal Cannizzaro dismutation. A free hydroxyl or amino group, *ortho* or *para* to the formyl group, interferes with the dismutation reaction, and prevents cleavage of the formyl group. These compounds yield the corresponding acid and alcohol in almost quantitative yield when the reaction is carried out in the presence of an active silver catalyst.¹⁰² *m*-Hydroxybenzaldehyde reacts normally, but *m*-dimethylaminobenzaldehyde fails to undergo the reaction.

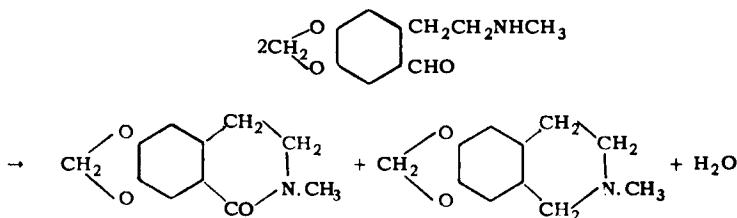
An aldehyde which carries substituents sensitive to alkali may undergo other changes involving these groups. *o*-Acetylaminobenzaldehyde, for example, undergoes an intramolecular condensation to form 2-hydroxyquinoline:¹⁰³



Opianic acid is converted into meconine and hemipinic acid, while *pseudo* opianic acid is deformylated:¹⁰⁴



Hydrastinine subjected to the Cannizzaro reaction gives the inner amide of the expected acid and hydrohydrastinine:¹⁰⁵



Crossed Cannizzaro Reaction¹⁰⁶

A crossed Cannizzaro reaction, carried out with equivalent amounts of the aromatic aldehyde and formaldehyde, results in the formation of both expected acids and alcohols. If, on the other hand, formaldehyde is used in excess, the aromatic alcohol is obtained in good yield with only a small quantity of the corresponding acid. The method has considerable preparative value for this reason.

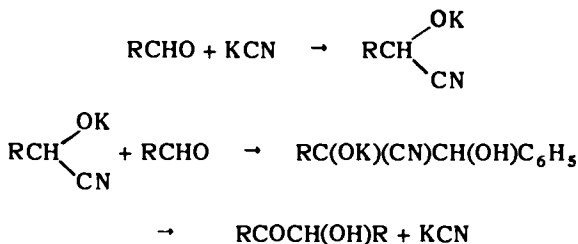
The reaction is carried out in the following manner: One molecular equivalent of the aromatic aldehyde, 700 cc of methyl alcohol, and 100 cc of formalin are mixed and heated to 65°; a solution of 120 gm of sodium hydroxide in 120 cc of water is rapidly added to the mixture with stirring, the temperature being maintained between 65 and 75° during the addition of the caustic. The mass is then cooled, diluted with 300 cc of water and the oily layer is separated. A certain amount of the product may be recovered from the aqueous layer by extraction with benzene. The product after drying may be purified by distillation under reduced pressure. Yields range between 85 and 95% of the theoretical.

Benzoin Condensation¹⁰⁷

On treatment of aromatic aldehydes with an alkali cyanide, self-condensation may occur resulting in the formation of an aromatic hydroxy ketone:



The reaction apparently involves the addition of the alkali cyanide to a molecule of the aldehyde, and the interaction of the addition compound with a second molecule of the aldehyde:¹⁰⁸



The procedure employed in carrying out the reaction is as follows: Two-tenths molecular equivalents of the aldehyde are dissolved in 100 cc of 95% ethyl alcohol, and 30 gm of a 33% aqueous potassium cyanide is added to the solution. The mixture is heated on a water bath under reflux for one to one and a half hours. After completion of the reaction, the mixture is diluted and cooled, and the product is filtered and purified by crystallization from alcohol or from acetic acid.

Magnesium and aluminum also induce the benzoin condensation.¹⁰⁹

Many substances inhibit the reaction, among them alkali halides, sulfur, hydrogen sulfide, carbon disulfide, thiobenzaldehyde, and hydroquinone.¹¹⁰ Alcohols accelerate the reaction in proportion to the number of hydroxyl groups present in their molecule.¹¹¹ Inhibitors are removed from the aldehyde by washing with aqueous carbonate or by treatment with solid potassium cyanide overnight at room temperature in an atmosphere of nitrogen; or the aldehyde may be purified as the bisulfite compound. The effect of impurities may be minimized by increasing the proportion of the water or by use of an excess of cyanide.

All aromatic aldehydes do not undergo the benzoin condensation; the reaction takes place if the aldehyde contains a relatively reactive carbinol group and a mobile hydrogen.¹¹² Ethers of hydroxy aldehydes undergo the reaction readily, provided phenolic impurities are absent,¹¹³ but hydroxy, halo, and amino aldehydes do not readily form benzoin. Many methoxybenzaldehydes containing additional alkoxy or other substituents have failed to give benzoin, although a benzoin has been obtained in 50% yield from 5-bromo-2-methoxybenzaldehyde.

Ortho-nitrobenzaldehyde gives a benzoin, but *meta* and *para* isomers give nitrophenylacetic acid and azobenzoic acid when subjected to the conditions of the reaction. 4-Cyanobenzaldehyde reacts to form a desoxybenzoin. Cinnamaldehyde gives a benzoin in very low yield. 4-Phenylbenzaldehyde gives a benzoin in good yield, but a low yield of the condensation product is obtained from α -naphthaldehyde.

Good yields of acyloin have been obtained from α -pinacolinaldehyde, quinaldehyde; 2-furaldehyde gives an acyloin in a moderate yield.

Unsymmetrical Benzoin

Aldehydes which do not undergo self-condensation to a benzoin may react with other aldehydes to form mixed or unsymmetrical benzoin. Two aldehydes

neither of which are capable of self-condensation, may react to form mixed benzoin, one having a reactive carbonyl group acting as an acceptor and the other containing a mobile hydrogen, acting as a donor of a hydrogen atom. Unsymmetrical benzoin, have been obtained with 2-chlorobenzaldehyde and the following: 4-methoxy-, 3-methoxy-4-ethoxy-, 3,4-diethoxy-, 3,4-dimethoxy-, and 3-ethoxy-4-ethoxybenzaldehyde. 4-Dimethylaminobenzaldehyde is also capable of forming mixed benzoin.

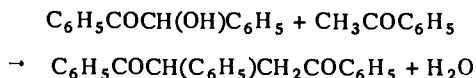
Two isomeric unsymmetrical benzoin, may be expected to result from the condensation of two different aldehydes. Only one isomer is usually obtained however. The carbinol group in the benzoin formed is usually adjacent to the unsubstituted phenol group or to a halogen-substituted phenyl group. The carbonyl group is usually adjacent to the methylenedioxy, 4-dimethylamino, methoxy, dimethoxy, methoxyethoxy, or diethoxy substituted aromatic ring, or to the furan nucleus, if condensation is between an aromatic aldehyde and furfuraldehyde.

Oxidative degradation or alkali fission convert benzoin into substituted benzaldehydes and benzoic acid.¹¹⁴ The oxime of a benzoin is oxidized with nitric acid to an aldehyde and an aryl nitrolic acid.

The oxime of a benzoin, subjected to the Beckmann rearrangement, gives an aldehyde, a nitrile, and an isonitrile:



Benzoin condenses with acetophenone under the action of potassium cyanide to form desylacetophenone:¹¹⁵



The hydroxyl group in benzoin is replaceable with amino groups. N-Pyridyl decylamine, $\text{NC}_5\text{H}_5\text{NHCH(C}_6\text{H}_5\text{)COC}_6\text{H}_5$, may be obtained, for example, from benzoin and 2-aminopyridine.²⁵⁸ This is known as the *Voigt reaction*.

Condensation Reactions with Compounds Containing a Reactive Methyl or Methylene

Aromatic aldehydes combine with many substances containing a reactive methyl or methylene group, in the presence of the appropriate condensing agents; they combine with aldehydes, ketones, mono- and dicarboxylic acids, etc. The reaction resembles aldol condensation, but in most cases water is lost, with the formation of an unsaturated body. Examples of such reactions are presented by the formation of cinnamic acid from benzaldehyde and acetic acid; cinnamaldehyde and benzalacetone from the same aldehyde by reaction with acetaldehyde and acetone respectively. The usual condensing agents employed are hydrogen chloride, sulfuric acid, zinc chloride, a mixture of acetic acid and acetic anhydride, dilute aqueous caustic, and sodium ethoxide. These reactions have been considered in detail in Chapter 5.

Aromatic aldehydes are also capable of giving condensation products with

aromatic compounds. Benzaldehyde and dimethylaniline react to give phenylbis-(*p*-dimethylaminophenyl)methane:



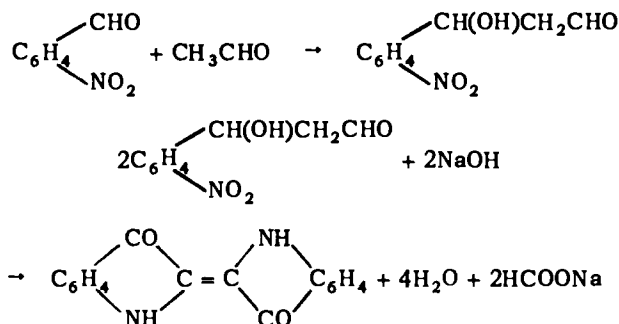
Phenols also give similar triphenylmethane derivatives with aromatic aldehydes.

Ring Compounds from Aromatic Aldehydes

The condensation of *o*-amino aldehydes with aldehydes, ketones, and acids results in the formation of heterocyclic compounds. Quinoline results, for example, from *o*-aminobenzaldehyde and acetaldehyde, and quinaldine is obtained from the same aldehyde by reaction with acetone. Quinazoline is formed through the condensation of *o*-aminobenzaldehyde with urea.¹¹⁶ Alcoholic ammonia converts acyl-*o*-aminobenzaldehydes into quinazolines. With hippuric acid azlactones or oxazolones are formed; these compounds are converted to α -amino acids with two carbon atoms more than the original aldehyde. Pyridine derivatives are formed when benzaldehyde and acetoacetic ester are made to condense with ammonia and aniline, although benzylidenedi-acetoacetic esters are obtained when aliphatic amines are used in the reaction.¹¹⁷

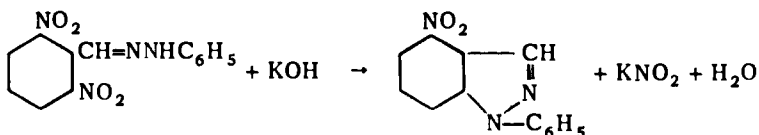
Benzaldehyde condenses with ketones of the type of diethyl ketone, forming diphenyl pyrones. With cyclic ketones in which the group $-\text{CH}_2\text{COCH}_2-$ forms part of the ring, dibenzylidene derivatives are obtained.²⁵⁵

o-Nitrobenzaldehyde reacts very readily with acetaldehyde under the action of dilute caustic to form *o*-nitrophenylhydracrylic aldehyde, which is converted by alkalis to indigo:

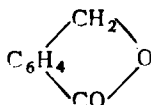


Acetaldehyde may be replaced with acetone in this reaction.

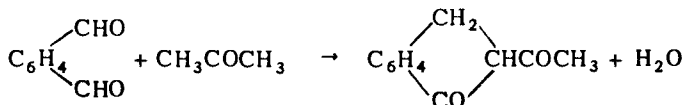
The phenylhydrazones of 2,6-dinitro- and 2,4,6-trinitrobenzaldehyde, heated with alcoholic potassium hydroxide, are converted into nitrated 1-phenylindazoles:²⁴⁹



Phthalaldehyde is converted to phthalide,



when treated with caustic. The aldehyde reacts with acetone to form β -acetylhydrindone:

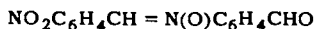


Similarly, β -benzoylhydrindone is obtained through the reaction of the aldehyde with benzophenone.

Reduction and Oxidation of Aromatic Aldehydes

Nascent hydrogen reduces aromatic aldehydes to alcohols and to hydrocarbons, the latter forming through the reduction of benzoin formed in the course of the reaction.¹¹⁹ Acetals of aldehydes in which the CHO group is attached to the aromatic nucleus may be reduced catalytically to aromatic hydrocarbons.¹²⁰

Reduced electrolytically in sulfuric acid, *m*- and *p*-nitrobenzaldehydes are converted to aldehydophenylhydroxylamines, $\text{OHC}_6\text{H}_4\text{NHOH}$; these combine immediately with unchanged nitroaldehyde, forming aldehydophenylnitro-*N*-benzaldoximea,



o-Nitrobenzaldehyde is also reduced to a hydroxylaminobenzaldehyde which, however, is very unstable and undergoes an internal condensation to form anthranil. This transformation also takes place with other nitro aldehydes in which the nitro and formyl groups are in ortho position to each other.

Aromatic aldehydes are readily oxidized to the corresponding acids. Oxidation often takes place gradually on exposure to atmospheric oxygen. Diphenylacetaldehyde, $(\text{C}_6\text{H}_5)_2\text{CHCHO}$, is oxidized to benzophenone, $(\text{C}_6\text{H}_5)_2\text{CO}$.¹²⁵ These aldehydes reduce alkaline silver nitrate, although they do not affect alkaline copper sulfate. Phenolic aldehydes are more resistant to oxidizing agents; they are best converted to carboxylic acids by fusion with a mixture of potassium hydroxide and lead dioxide. Ortho and parahydroxyaldehydes are oxidized by caustic potash at moderate temperature, but metahydroxybenzaldehyde, treated with caustic, undergoes the Cannizzaro reaction giving equal amounts of the corresponding acid and alcohol. Methyl ethers of *o*- and *p*-hydroxybenzaldehydes also undergo this transformation.¹²¹ Dilute alkaline hydrogen peroxide readily oxidizes *o*- and *p*-hydroxyaldehydes to pyrocatechol and hydroquinone respectively, the aldehyde group being cleaved in the process.¹²²

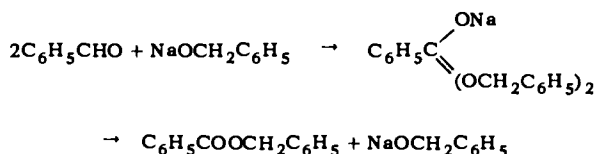
Treatment of aromatic aldehydes with chlorine results in the replacement of the hydrogen in the aldehyde group with chlorine.

Isomerization and Dimerization

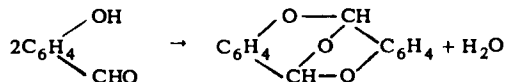
Orthonitrobenzaldehyde, dissolved in an indifferent solvent and exposed to the action of sunlight, undergoes rearrangement to form *o*-nitrosobenzoic acid. The same transformation takes place when the compound is treated with an ammoniacal solution of ammonium cyanide.¹²³ In alcoholic solution, esters of *o*-nitrosobenzoic acid are formed, acetals apparently being formed as intermediates. This transformation does not take place if another substituent is present in *ortho* position.¹²⁴

Aldehydes of the type ArCH(Alk)CHO are transformed on heating into ketones of the type $\text{ArCH}_2\text{COAlk}$.²⁵⁰

Benzoin condensation constitutes a dimerization of aldehydes; another type of dimerization involving aromatic aldehydes is the formation of benzylbenzoic esters on heating aromatic aldehydes with a small amount of sodium benzoate.¹²⁶ In this reaction, an orthobenzylbenzoate is probably formed as an intermediate:



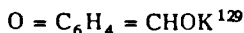
Salicylaldehyde in solution is rapidly dimerized to a cyclic inner acetal under the action of a very small amount of mineral acid:¹²⁷



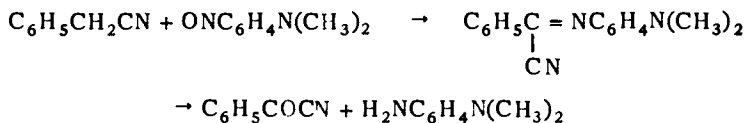
Aromatic aldehydes generally form insoluble complexes with alkaline-earth metal salts of aromatic amino carboxylic or amino sulfonic acids.²⁵⁷ The aldehyde may be regenerated from these complexes by steam distillation. The complexes can, therefore, serve for the isolation of aromatic aldehydes.

Some Characteristics of Phenolic Aldehydes

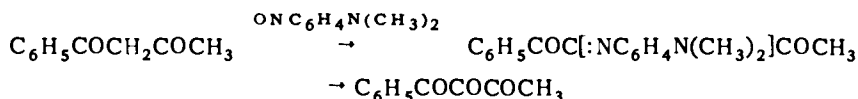
The phenolic hydrogen in salicylaldehyde is linked to the oxygen of the aldehyde group by coordinate valencies to form a chelate compound.¹²⁸ *o*-Hydroxy aldehydes are volatile with steam, and give difficultly soluble sodium bisulfite compounds. The presence of the formyl group in *o*-hydroxy aldehydes greatly increases the acidity of the hydroxyl group so that these aldehydes are soluble in aqueous sodium carbonate solution. Phenol aldehydes form two series of salts: colorless salts of the normal type, such as $\text{OCHC}_6\text{H}_4\text{OK}$, and colored salts, usually yellow, with a quinoid structure, such as



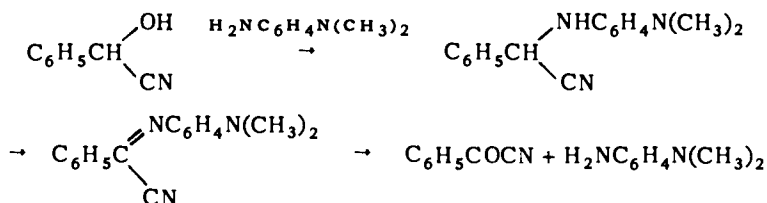
The phenylhydrazone of homosalicylaldehydes and other ring-alkylated salicylaldehydes are insoluble in aqueous alkalis.¹³⁰ The presence of a hydroxyl group in the *ortho* position to the aldehyde group diminishes the tendency toward molecular association, whereas the presence of a hydroxyl group in the *para* position increases this tendency.



Phenyl methyl triketone, $\text{C}_6\text{H}_5\text{COCOCOCH}_3$, has been prepared from benzylacetone by reaction with nitrosodimethylaniline and decomposition of the dimethylaminoanil formed:



Secondary alcohols, such as phenylmethylcarbinol, may be converted to ketones by oxidation, or by an exchange reaction with an aldehyde or ketone.¹³⁸ Oxidation may be carried out, in an indirect manner, in the case of aromatic cyanohydrins, by replacement of the hydroxyl group with the dimethylamino aniline group, oxidation to the anil, and hydrolysis of the latter:



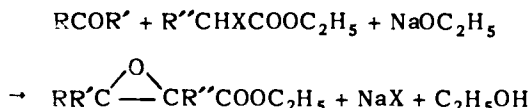
Isomerization of Epoxy Compounds; other Isomerizations

Ketones may be obtained by the isomerization of ethylenic oxides; phenylpropylene oxide, for example, gives benzyl methyl ketone when heated:¹³⁹



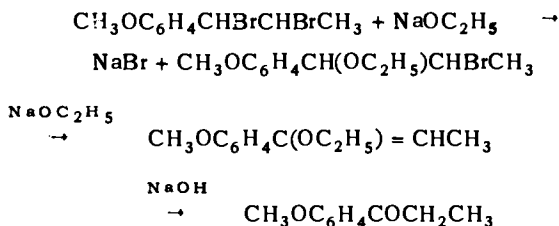
Transformation of certain ethylene glycols to ketones by heating with dilute acids may be considered to proceed via the oxide stage.

Aromatic glycidic acids of the type $\text{R}^1\text{R}^2\text{C} \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \end{array} \text{CR}^3\text{COOH}$ have also been transformed by heat into ketones, $\text{RR}'\text{CHCOR}''$, by loss of carbon dioxide.¹⁴⁰ Esters of such acids are readily obtained through the condensation of aldehydes or ketones with α -halo esters:¹⁴¹

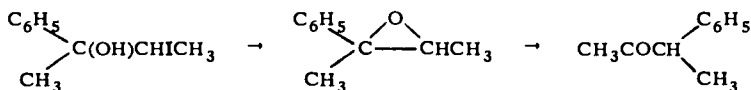


The ester may be conveniently converted to the sodium salt of the acid by treatment with the exact equivalent of sodium ethoxide followed by the addition of water. Subsequent addition of ether causes the precipitation of the sodium salt of the acid.

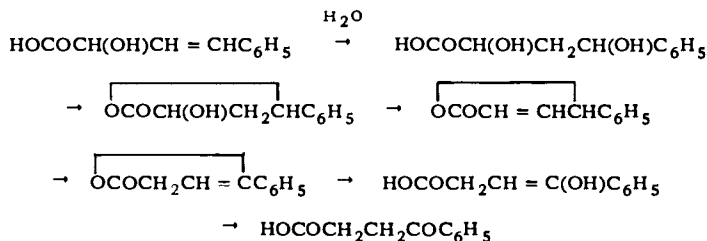
Transformation of dibromides of aromatic olefinic compounds into ketones may be effected by conversion to the ethyl ether of the bromohydrin, dehydrobromination of the latter, followed by hydrolysis of the resulting ethoxy olefin:



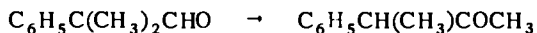
Iodohydrins of certain arylated olefins, treated with silver nitrate or mercuric oxide, yield ketones as a result of the isomerization of the epoxide initially formed. The transformation involves a migration of the aromatic group:



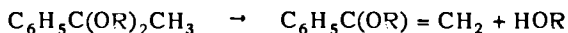
The ready formation of a keto acid on treatment of β -benzylidene- α -hydroxypropionic acid with hydrochloric acid involves an isomerization probably similar to that of epoxides into ketones:



Arylated aliphatic ketones of the type ArCH(R)COR are formed by the action of concentrated sulfuric acid on disubstituted aromatic aldehydes, $\text{ArCRR}'\text{CHO}$, one alkyl group migrating to the carbonyl group. Thus, phenyldimethylacetaldehyde gives 2-phenylbutane-3-one:¹⁴²



Ethers of phenylolefinic alcohols undergo rearrangement to form ketones. Ethers of this type result on heating ortho ethers of acetophenone:¹⁴³



Rearrangement of the olefinic ethers gives acylbenzenes



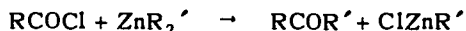
Distillation of certain tertiary phenyl carbinols, ArC(R)(OH)Alk , under reduced pressure results in the formation of ketones, ArCOR , with cleavage of the hydrocarbon AlkH .¹⁴⁴

Ketones from Acids, Acid Chlorides, and Nitriles

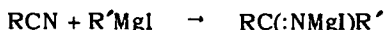
The dry distillation of a mixture of the calcium salts of an aromatic and an aliphatic acid results in the formation of an aromatic ketone.¹⁴⁵ Ketone forma-

tion may be brought about directly by passing vapors of the aromatic acid mixed with those of the aliphatic acid over manganese oxide or thoria heated to 460° .¹⁴⁶

Aromatic ketones may be obtained through the interaction of an aromatic acid chloride with a zinc alkyl:¹⁴⁷



Halomagnesium derivatives of aromatic ketimines are formed through the reaction of alkyl magnesium halides with aromatic nitriles:¹⁴⁸

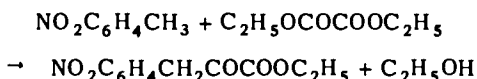


These may be converted to ketones, RCOR' , by hydrolysis. *p*-Diacetylbenzene has been obtained by this method from terephthalic nitrile and methylmagnesium iodide.¹⁴⁹ This subject has been covered in Chapter 12 dealing with the Grignard reaction.

Aryl cyanates, RCNO , give ketoximes by reaction with alkyl magnesium halides.¹⁵⁰

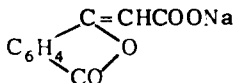
Ketones by Condensation Reactions

Aromatic ketones may be formed through ester condensation with compounds containing a reactive methyl or methylene group. Thus benzoylacetic ester, $\text{C}_6\text{H}_5\text{COCH}_2\text{COOC}_2\text{H}_5$, and benzoylpropionic acid, $\text{C}_6\text{H}_5\text{COCH}(\text{CH}_3)\text{COOC}_2\text{H}_5$, may be obtained by this method; these compounds may be converted to acetophenone and propiophenone respectively by ketone hydrolysis.¹⁵¹ Condensations of this type with ketones lead to the formation of diketones.¹⁵² The reaction of *o*- or *p*-nitrotoluene with oxalic ester in the presence of sodium ethoxide gives the ester of *o*- or *p*-nitrophenylpyruvic acid:¹⁵³



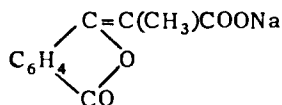
The reaction of aromatic acid chlorides with the sodio derivatives of acetoacetic ester and other compounds with a reactive methylene also give keto compounds. Thus, benzoylacetoacetic ester, $\text{C}_6\text{H}_5\text{COCH}(\text{COCH}_3)\text{COOC}_2\text{H}_5$, may be obtained by this method from benzoyl chloride and the sodio derivative of acetoacetic ester. Ketonic hydrolysis of benzoylacetoacetic ester gives an aromatic diketone. The hydrolysis of terephthalyl-bis-acetoacetic ester gives *p*-diacetylbenzene.¹⁵⁴

The condensation of phthalic anhydride with sodium acetate in the presence of acetic anhydride gives the sodium salt of phthalylacetic acid



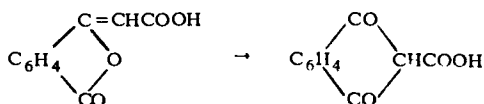
This compound is converted to the sodium salt of benzoylacetic *o*-carboxylic acid, $\text{NaOCOC}_6\text{H}_4\text{COCH}_2\text{COONa}$, when treated with an excess of cold caustic

solution. When the free acid in aqueous solution is heated to boiling, it is converted to acetophenone-*o*-carboxylic acid, $\text{HOCOC}_6\text{H}_4\text{COCH}_3$. The reaction is applicable also to the homologs of acetic acid: ¹⁵⁵ sodium propionate, for example, gives the sodium salt of phthalylpropionic acid,

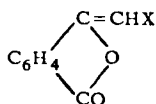


decarboxylation of the free acid leading to the formation of propiophenone-carboxylic acid, $\text{HOCOC}_6\text{H}_4\text{COCH}_2\text{CH}_3$.

Phthalylacetic acid undergoes molecular transformation under the action of sodium chloride, giving α,γ -diketohydrinone carboxylic acid:

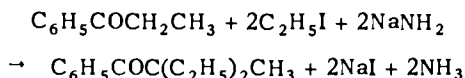


Other compounds of the type



also undergo an analogous transformation.

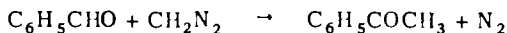
Aromatic ketones having a reactive methylene or methyl group may be modified through the introduction of other groups into their molecule by combination with this group. The hydrogen atoms of the methylene group adjoining the carbonyl group in aryl alkyl ketones may be replaced by alkyl groups, for example, by reaction with alkyl iodides in the presence of sodamide: ¹⁵⁶



Alkylated benzoylactic esters may be obtained through the interaction of alkyl halides with the sodium derivatives of benzoylactic ester. The mono and dialkylbenzoylactic esters may be converted to alkylated acetophenones, such as $\text{C}_6\text{H}_5\text{COCH}_2\text{C}_2\text{H}_5$ and $\text{C}_6\text{H}_5\text{COCH}(\text{C}_2\text{H}_5)_2$, by ketonic hydrolysis.

While the reaction of metal derivatives of benzoylactic ester with alkyl halides gives C-alkylated compounds, reaction with acyl halides results in the formation of O-acyl derivatives. Thus, acetyl chloride reacting with the copper compound of acetylbenzoic ester, gives largely β -acetoxycinnamic ester, $\text{C}_6\text{H}_5\text{C}(\text{OCOCH}_3)=\text{CHCOOC}_2\text{H}_5$, with only a small amount of benzoylacylactic ester.

Aromatic methyl ketones result through the reaction of diazomethane with an aromatic aldehyde: ¹⁵⁷

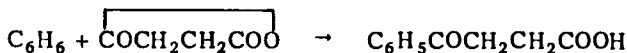
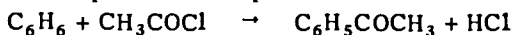


Triacetylbenzene, $C_6H_3(COCH_3)_3$, is formed through the self-condensation of acetoacetaldehyde.¹⁵⁸

Nuclear Syntheses

Ketones by Friedel-Crafts Reaction and its Variants

Aromatic ketones result through the reaction of acyl halides or acid anhydrides with aromatic compounds in the presence of aluminum chloride.¹⁵⁹



The reaction requires only gentle heating and proceeds very well with homologs of benzene. The acyl group preferentially enters the para position with respect to a substituent, and only in rare instances more than one acyl group enters the nucleus.¹⁶⁰ Ferric chloride and certain other metallic chlorides have also been used as catalysts in this reaction. Alkyl ethers of phenols undergo the reaction particularly well.¹⁶¹ The subject has been considered in detail in Chapter 13, dealing with Friedel-Crafts reaction.

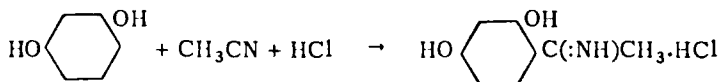
Phenols react readily with acid chlorides in the presence of zinc chloride or stannic chloride to form aromatic ketones.¹⁶²

Phenols react with acetic acid and aromatic acids in the presence of zinc chloride, stannic chloride, and especially well in the presence of phosphorus oxychloride, to form aromatic ketones.¹⁶³ The reaction is applicable to mono- and polyhydric phenols.

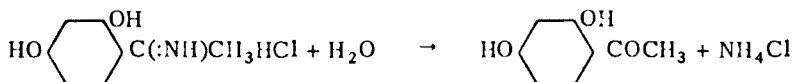
Phenolic ketones may be prepared by the *Fries rearrangement* involving the isomerization of phenol esters to acylphenols.¹⁶⁴ This reaction has been considered in Chapter 23, dealing with phenols.

Houben-Hoesch Synthesis

Nitriles react with meta di- and trihydric phenols in the presence of hydrogen chloride and the appropriate catalyst to form ketimine hydrochlorides, the ketimine group replacing a nuclear hydrogen in the aromatic compound:



The formation of ketimine is apparently preceded by the addition of a molecule of hydrogen chloride to the nitrile group, giving an iminochloride. Hydrolysis of the ketimine formed gives a keto compound.

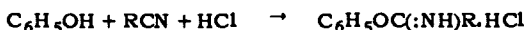


The reaction is known as the Houben-Hoesch Synthesis.¹⁶⁵

The usual procedure followed in carrying out the reaction is to dissolve equimolecular quantities of the nitrile and phenol in anhydrous ether containing the catalyst in suspension, and to pass a stream of dry hydrogen chloride through the solution cooled to 0° , for about half an hour. The mixture is allowed to stand for several hours, and if the imine hydrochloride is insoluble in ether, it may be separated by filtration and hydrolyzed; otherwise, water is added to the reaction mixture with good agitation, the aqueous layer is separated and heated. The ketone formed may be isolated by filtration or extraction with a solvent. Hydrolysis may be aided by the addition of ammonia, sodium hydroxide, dilute hydrochloric acid or sulfuric acid.

Zinc chloride and iron chloride are satisfactory catalysts in many cases; occasionally the more powerful catalyst aluminum chloride may have to be used.

When free phenols are employed in the reaction, imino ether hydrochlorides are sometimes formed as a by-product:



In some cases the imino ether hydrochloride is the principal product of the reaction. Phenol and β -naphthol give 42 to 74% yields of imino ethers with acetonitrile, phenylacetonitrile and benzonitrile.

The solvent has a decided influence on the readiness with which the reaction proceeds. Ether appears to be a satisfactory medium, but the reaction generally proceeds very slowly in most other solvents.¹⁶⁶

The Houben-Hoesch synthesis proceeds most readily with resorcinol¹⁶⁷ and other meta dihydroxyphenols, and with phloroglucinol. The ethers of these phenols also undergo the reaction quite readily. Orcinol reacts readily with acetonitrile, benzonitrile, and β -phenylpropionitrile, but not with succinonitrile; 1,2,4-trihydroxybenzene condenses with *p*-chlorobenzonitrile; pyrogallol also reacts with this nitrile but not with benzonitrile and succinonitrile. Catechol and hydroquinone apparently do not undergo the reaction.

The hydroxyl and alkoxy groups exert a *para* directing influence; the directive influence of the methoxy group is as strong as that of the hydroxyl group. Halogens in the *ortho* position with respect to a hydroxyl or methoxy group greatly hinder the reaction; on the other hand, a methyl group in the *ortho* position favors the reaction. A methyl group in *meta* position causes some decrease in the reaction rate, and one in *para* position greatly hinders the reaction. A carboxyl group in the *ortho* position reacts preferentially with the nitrile group to form an acylamine, $\text{RCON} = \text{CClR}'$.

As a general rule, a single ketimine group enters the aromatic nucleus; in only one instance, namely the reaction of acetonitrile with phloroglucinol, has the formation of a diketone been reported.¹⁶⁸ With phenol ethers only one isomer is often obtained when the formation of more than one isomer is expected; with certain ethers, however, two isomeric ketimines have been obtained.¹⁶⁹

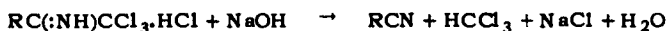
Aromatic nitriles react less readily than aliphatic nitriles.¹⁷⁰ Aliphatic dinitriles react with resorcinol and phloroglucinol less readily than mononitriles and usually give monoketonic acids as the final product of hydrolysis.¹⁷¹ Dinitriles have not been condensed successfully with other phenols. Only the aliphatically bound nitrile appears to react when the compound contains an aliphatically and aromatically bound nitrile group. Cyanogen reacts with resorcinol to give a mixture of tetrahydroxybenzil and dihydroxyphenylglyoxylic

acid;¹⁷² with orcinol and 2,4-dimethyl-3-carboxypyrrole, only glyoxylic acid derivatives have been obtained.

The Houben-Hoesch synthesis is applicable to cyanohydrins. Resorcinol reacting with formaldehyde cyanohydrin gives hydroxymethyl-2,3-dimethoxyphenylketimine.¹⁷³

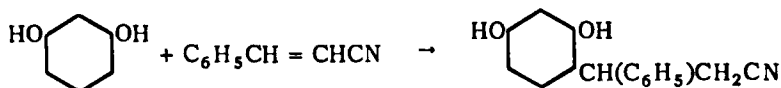
The reactivity of aromatic nitriles is decreased by some *ortho* substituents; *o*-cyano-, *o*-nitro-, *o*-chloro-, and *o*-methylbenzonitrile do not react with resorcinol or phloroglucinol. Substituents in the *meta* and *para* position in benzonitrile and benzyl cyanide do not generally affect the reactivity of the cyano group.

Trichloroacetonitrile undergoes the Houben-Hoesch condensation with unusual ease. In contrast with other nitriles, it is capable of condensing readily with benzene and its homologs, monohydric phenols and their ethers.¹⁷³ The ketimine hydrochlorides obtained may be readily decomposed with alkalis to a nitrile according to the following scheme:¹⁷⁴

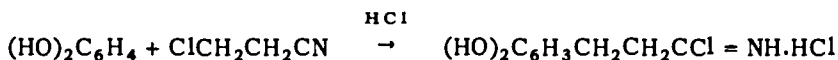


Abnormal Reactions; Ring Formations

Certain substituted nitriles fail to undergo the normal Houben-Hoesch reaction because of the presence in their molecule of one or more functional groups capable of reaction with the aromatic nucleus. α,β -Unsaturated nitriles react with phenols under the conditions of the reaction to form a saturated nitrile by addition of the aromatic group at the ethylenic bond:¹⁷⁵

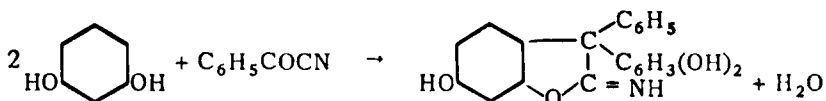


Hydrolysis of the compound leads to the formation of a dihydrocoumarin. Acrylonitrile reacts in a similar manner. β -Halo-, β -hydroxy-, β -carbethoxy-, β -benzoyloxy-, β -aldehydo-, β -keto-, and β -ketimino-nitriles also react in an abnormal manner. γ -Chloropropionitrile reacts with resorcinol to form γ -(2,4-dihydroxyphenyl)chloropropionimide chloride:¹⁷⁶



The chloroimine condenses to hydroxychromoneimide, from which hydroxychromanone is obtained by hydrolysis. γ -Hydroxypropionitrile reacts similarly.¹⁷⁶

Arylglyoxylic acids also react abnormally to form polyhydroxyphenylacetic lactones, from which the corresponding lactones may be obtained by hydrolysis:¹⁷⁷



Alkylglyoxylic nitriles react normally with resorcinol to form ketimines which give 1,2-diketones on hydrolysis.¹⁷⁸

Cyclic compounds may be formed from the ketimines obtained with certain nitriles. Chloroacetonitrile, for example, reacting with resorcinol, gives the ketimine of 5-hydroxycoumaronone;¹⁷⁹ with phloroglucinol, 2,4,6-trihydroxyphenylchloromethylketimine is formed, which, on hydrolysis and subsequent condensation under the action of sodium acetate, gives a dihydroxycoumaronone.¹⁸⁰ Ring formation is also observed with α -hydroxynitriles.

Dihydroxycoumarins are obtained through the reaction of ethyl cyanoacetate with resorcinol and phloroglucinol and hydrolysis of the ketimine formed.¹⁸¹

Coumarin derivatives have been obtained also from the condensation product of resorcinol with *p*-methoxybenzoylacetonitrile, $\text{CH}_3\text{OC}_6\text{H}_4\text{COCH}_2\text{CN}$,¹⁸² ethyl phenylcyanopyruvate,¹⁸³ and formylphenylacetonitrile, $\text{C}_6\text{H}_5\text{CH}(\text{CHO})\text{CN}$.¹⁸⁴

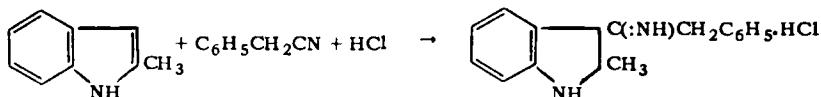
An isoflavone has been obtained through the internal condensation of resorcinol-acetophenone cyanohydrin and hydrolysis of the product; *pseudo*-patigenin has been obtained in a similar manner.¹⁸⁵ 2,3,6,7-Dimethylenetetraoxanthraquinone diimide has been obtained through the self-condensation of piperonylic nitrile under the conditions of the Houben-Hoesch synthesis.¹⁸⁶

Extension of Houben-Hoesch Synthesis

Acenaphthene has been condensed with cyanoacetic acid in the presence of sodium aluminum chloride to a ring ketimine, with the keto and ketimine groups at 4 and 5 positions.¹⁸⁷

Anthranol methyl ether reacts with acetonitrile in the presence of aluminum chloride to form 10-methoxy-9-anthryl methyl ketimine.¹⁸⁸ The latter is converted to an anthrone when heated with 2-normal hydrochloric acid. Depsenones have been obtained through the condensation of 2-methyl-5-hydroxycoumarone with various nitriles.¹⁸⁹ Tetrahydroeuparin has been obtained by the condensation of 6-hydroxy-2-isopropylcoumarin with acetonitrile and subsequent hydrolysis of the ketimine.¹⁹⁰

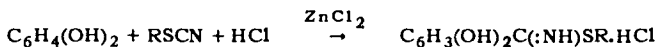
The Houben-Hoesch synthesis has been applied successfully to *pyrrole* and its derivatives.¹⁹¹ Condensation has been effected both with aliphatic and aromatic nitriles. 2-Methylindole gives excellent yields of a ketimine with benzyl cyanide:¹⁹²



Good yields of ketimines are obtained also with ethyl cyanoacetate and benzoyl cyanide.

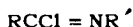
The reaction has been extended to *cyanogen bromide*. The product of the reaction with resorcinol, after hydrolysis, is 2,4-dihydroxybenzaldehyde.¹⁹³

The synthesis has been applied also to *thiocyano* and *isothiocyano* compounds. Thiocyanates react normally to form iminothiol esters:¹⁹⁴

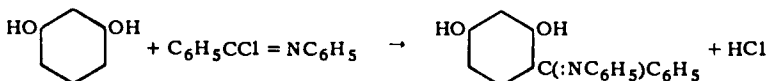


Isocyanates yield compounds of the type RCSNHR .¹⁹⁵

The Houben-Hoesch type synthesis has been carried out with iminochlorides,



Benzanilide iminochlorides have been condensed with resorcinol to form Schiff bases:¹⁹⁶



The bases may be readily converted to the corresponding ketones by hydrolysis.

Aromatic Ketones with other Functional Groups

Phenolic ketones may be prepared by the general methods employed for the preparation of phenols; in effect, two of the methods, namely the Friedel-Crafts synthesis and the Houben-Hoesch condensation, are applicable primarily to phenolic compounds or their derivatives. They may be obtained further from amino ketones by replacement of the amino group by a hydroxyl group, and by heating halo ketones with strong bases under pressure in the presence of cuprous oxide.¹⁹⁷

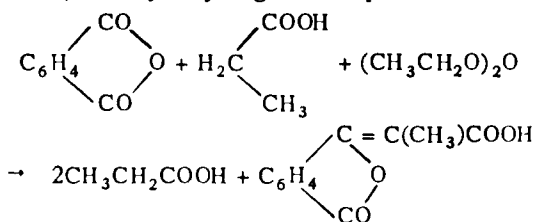
Halo aromatic ketones may be prepared by the Friedel-Crafts reaction from halo aromatic compounds and acyl chlorides.¹⁹⁸

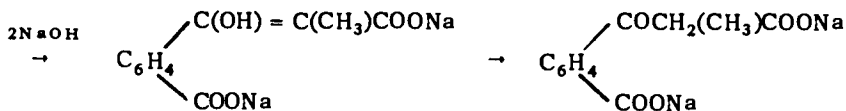
The direct *nitration* of certain aromatic ketones can be carried out successfully with certain ketones; thus acetophenone can be nitrated to *m*-nitroacetophenone at a low temperature.²⁵¹ With rising temperature the yield of nitroacetophenone decreases through the formation of the isonitroso derivative.²⁰⁰ The three isomeric nitroacetophenones have been obtained from the corresponding nitrobenzoylacetoacetic esters by ketonic hydrolysis.²⁰¹ *p*-Nitroacetophenone has been obtained by hydration of *p*-nitropropionic acid with concentrated sulfuric acid.²⁰² *p*-Nitrosophenylacetylene is first formed in this reaction and is subsequently converted to the nitro ketone. *m*-Dinitroacetophenone has been obtained by the action of sulfuric acid on *m*-dinitrobenzoylacetic acid ester.²⁰³

Aminoacetophenones, $\text{H}_2\text{NC}_6\text{H}_4\text{COCH}_3$, have been obtained through the reduction of nitroacetophenones,²⁰⁴ the *ortho* isomer has also been prepared from *o*-aminophenylpropionic acid by hydration and decarboxylation with boiling water, and by the treatment of *o*-aminophenylacetylene with concentrated sulfuric acid.²⁰⁵

Some of the general methods described for the preparation of aromatic ketones are applicable to the preparation of ketones with *carboxyl* groups in the aromatic radical.

Aromatic keto acids in which the carboxyl group is in *ortho* position to the keto group may be obtained by condensing phthalic anhydride or a substituted phthalic anhydride with sodium acetate or propionate in the presence of the anhydride of the acid, and hydrolyzing the compound formed with alkalis:²⁰⁶





Partial decarboxylation of the free dicarboxylic acid gives a keto acid:

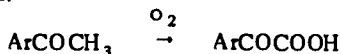


Phthalonic acid, $\text{C}_6\text{H}_4(\text{OOH})\text{COCO}(\text{OOH})$, results when sodium α -naphtholate in aqueous solution is oxidized with potassium permanganate. The compound is formed also when naphthalene is oxidized with manganates or permanganates.²⁰⁷

Arylglyoxylic acids, $\text{ArCOCO}(\text{OOH})$, are obtained in the form of their esters through the reaction of aromatic compounds with ethoxalyl chloride,



in the presence of aluminum chloride.²⁰⁸ They may be prepared also by oxidizing the methyl group in acetophenone and its derivatives with cold alkaline permanganate solution:²⁰⁷



Aryl methyl ketones can be converted to arylglyoxylic nitriles by reaction with amyl nitrite in the presence of sodium ethylate, and dehydration of the resulting isonitroso ketone with acetic anhydride:²⁰⁹



α -Keto carboxylic acids can be obtained further by the oxidation of glycols, keto alcohols, and α -hydroxy carboxylic acids.

Phenylpyruvic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{COCO}(\text{OOH})$, is obtained by boiling phenylloxalacetic ester, $\text{C}_6\text{H}_5\text{CH}(\text{COOH})\text{COCOOC}_2\text{H}_5$, with dilute sulfuric acid; it can also be obtained from α -benzoylaminocinnamic acid by boiling with aqueous caustic or hydrochloric acid. It is believed that the free acid exists in the enolic form, while the salts have the keto structure.²¹⁰

β -Keto carboxylic acids result through the reaction of benzoic esters with aliphatic esters in the presence of sodium ethoxide. They may be obtained also by the reaction of aryl halides with acetoacetic ester in the presence of sodium ethoxide or metallic sodium; by the reaction of benzaldehydes with diazoacetic ester; and by the reaction of malonic ester halides, $\text{ROCOCH}_2\text{COCl}$, with aromatic compounds in the presence of aluminum chloride.²¹¹ The reaction of benzoyl halides with α -halomagnesium aliphatic esters,²¹² and the hydration of aryl propiolic esters also gives β -keto acids in the form of their esters.

Many β -keto esters have been synthesized by the action of diethyl carbonate on the sodio derivative of a ketone:²¹³



The sodio derivative of the ketone is obtained through the reaction of the ketone with sodamide. An excess of sodamide favors the condensation.

Phenol keto carboxylic acids of the type $(\text{HO})_2\text{C}_6\text{H}_3\text{CO}(\text{CH}_2)_n\text{COOH}$ are obtained through the condensation of phenols with dicarboxylic acids,



in the presence of zinc chloride.²¹⁴ Reduction of these acids with amalgamated zinc and hydrochloric acid results in the formation of arylaliphatic acids.

Behavior and Reactions of Aromatic Ketones

The carbonyl group in aromatic ketones resembles that in aldehydes in its characteristics, though it is much less reactive than the carbonyl group in aldehydes.

Reaction with Hydroxylamine

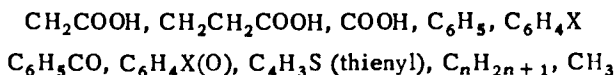
Aromatic ketones react with hydroxylamine to form ketoximes.²¹⁵

With the more reactive ketones, reaction proceeds on shaking an aqueous solution of hydroxylamine with the ketone at room temperature. Good results are obtained when the solution is buffered with a mixture of sodium acetate and acetic acid. The condensation may also be effected by use of hydroxylamine or its salts in liquid ammonia.²¹⁶ The more resistant ketones are heated in a sealed tube with an alcoholic solution of hydroxylamine. The reaction is favored by alkalis, so that when a very large excess of alkali is employed the reaction almost always proceeds at room temperature.²¹⁷

The readiness with which the reaction takes place is influenced by the structure of the ketone.²¹⁸ The rate of reaction of ketones with *ortho* substituents may be ten to hundred times as great as with the *para* isomer. Hydroxyl or methoxy groups in the *para* position materially increase the reaction rate. Compounds in which the carbonyl group is situated between two *ortho* substituents are resistant to oximation.²¹⁹

Aromatic α -diketones, ArCOCOAlk , are capable of yielding two different types of oximes, the α -form, $\text{ArC}(\text{:NOH})\text{COAlk}$, and the β -form, $\text{ArCO}(\text{:NOH})\text{Alk}$. Benzil, for example, gives α -benzil monoxime rapidly at -5° by reaction with hydroxylamine in the presence of sodium hydroxide. The usual method of oximation with one equivalent of hydroxylamine yields the β -form. Oximes of the α -form may be prepared indirectly. The α -monoxime of acetylbenzoyl may be obtained, for example, by nitrosation of phenylacetone with isoamyl nitrite.²²⁰ The ketone and its equivalent of sodium ethoxide are dissolved in alcohol and the equivalent of nitrous ester is added at a low temperature; after 24 hours or more, the product can be separated by dilution with water, and precipitation of the oxime by addition of a mineral acid, after the extraction of alkali soluble impurities. The second oxime group is not introduced so readily, and to obtain the dioxime, the ketone must be heated in solution with an excess of hydroxylamine.

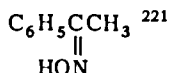
The stability of isomeric oximes derived from ketones XCOY varies according to the nature of the groups X and Y. The attractive power of various groups for the OH group in the oxime ranges in descending order as follows:



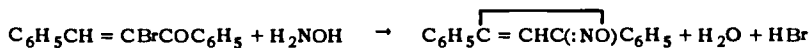
The closer the two groups present in the oxime, in this series, the greater is

the probability that the two isomeric modifications vary little in their stability.

Oximes of the fatty aromatic series are known only in the *anti* alkyl configuration, benzophenone, for example giving

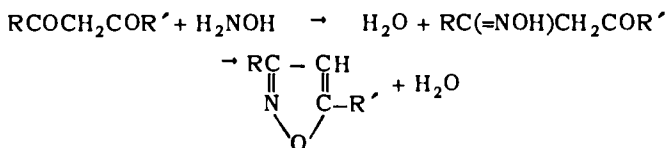


Benzoylbromostyrene, treated with an alkaline solution of hydroxylamine, gives 3-5-diphenylisoxazole:²²²

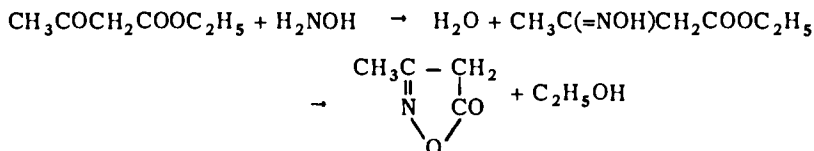


The reaction of hydroxylamine with β -keto acids gives oximes, anhydrides, lactoximes, or isoxazolones.

β -Diketones do not give oximes with hydroxylamine, but react to form isoxazoles:²²³

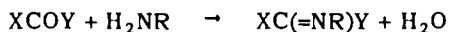


In a similar manner, isoxazolones result from the reaction of hydroxylamine with β -keto esters:



Oximes are soluble in aqueous caustic, but are precipitated from solution by carbon dioxide. Oximes are weakly basic and their hydrochlorides are extensively hydrolyzed in aqueous solution. They are hydrolyzed by mineral acids to hydroxylamine and the corresponding ketone, but are not attacked by caustic. They may be hydrogenated to amines by a variety of methods, including electrolytic reduction or reduction with sodium amalgam in alcoholic solution.

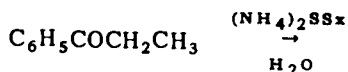
Aromatic carbonyl compounds react with amines to form imines:



Ketones do not readily react in this manner, however, with aniline bases.²²⁴ The condensation products with fatty aromatic ketones are much less stable than Schiff bases proper. Stereoisomerism has not, thus far, been observed with anils of the type $\text{XC}(\text{=NOH})\text{Y}$.

Willgerodt Reaction

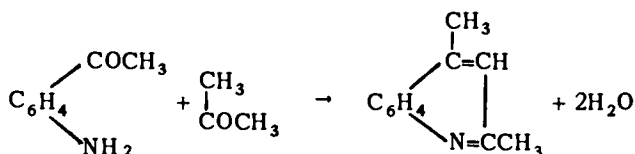
Alkyl aromatic ketones heated at 250° with yellow ammonium sulfide give an amide, with a smaller amount of the ammonium salt of the corresponding acid, as a result of an internal rearrangement:²²⁵



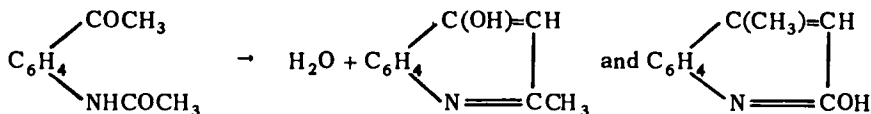
This is known as the Willgerodt reaction. The proportion of acid formed decreases with increase in the number of carbon atoms of the side chain, phenyl heptyl ketone giving no acid. The Willgerodt reaction has been dealt with under Chapter 5.

Ring Compounds from *o*-Amino Ketones

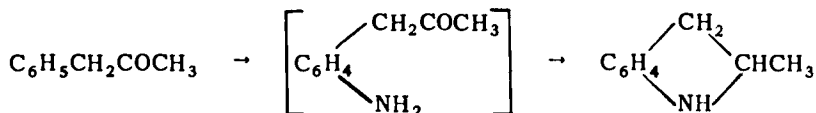
o-Aminoacetophenone condenses with acetone in the presence of sodium hydroxide to form dimethylquinoline:²²⁶



o-Acetylaminacetophenone undergoes self-condensation in the presence of sodium hydroxide to *o*-methyl- γ -hydroxy- and *o*-hydroxy- γ -methylquinoline:²²⁷



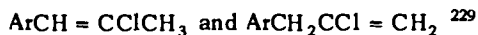
Nitration of phenylacetone followed by reduction results in the formation of dihydro- β -methylindole:²²⁸



Similar treatment of benzylacetone results in the formation of tetrahydroquin-aldine. The intermediate compounds are probably *o*-amino alcohols, rather than amino ketones.

Reaction with Phosphorus Halides

The reaction of phosphorus pentachloride with aromatic ketones of the type $\text{ArCH}_2\text{COCH}_3$ results in the formation of a mixture of chloro olefins,



Aromatic ketones of the type of acetophenone give principally chloroethylene and a polymeric compound. Chlorostyrene is obtained in 54% yield from acetophenone when the reaction is carried out in petroleum ether, and the phosphorus pentachloride is mixed with coarsely broken glass.²³⁰

o-Bromo ketones are formed when phosphorus pentabromide is made to react with aromatic or other types of ketones.

Oxidation and Reduction of Aromatic Ketones

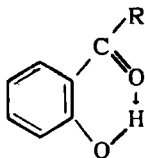
Aromatic ketones, ArCOR , are converted to acids, ArCOOH , when oxidized with chromic acid mixture. α -Keto carboxylic acids are obtained when such ketones are oxidized with potassium permanganate.²³¹ α -Keto acids, RCOCO_2H , are oxidized to simple acids, RCOOH ; such acids appear to be less susceptible to oxidation if the ortho position in the aromatic nucleus is occupied by an alkyl group.

Secondary alcohols may be obtained through the partial reduction of ketones.²³² Alkyl benzenes are obtained through the reduction of alkyl aromatic ketones by Clemmensen's method; i.e., by use of amalgamated zinc and hydrochloric acid.²³³ This subject has been treated under Chapter 4.

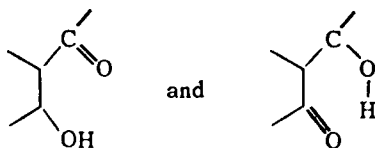
The hydrogen atoms in the alkyl group of an aromatic ketone may be replaced, all or in part, by chlorine, by the action of alkali hypochlorites.²³⁴

Chelation of o-Hydroxy Aromatic Ketones

Aromatic o-hydroxy ketones, in common with aromatic o-hydroxy aldehydes and nitro compounds, are capable of chelation.²³⁵ An essential requirement for the formation of a chelate compound is that a double bond be present between the carbonyl and hydroxyl groups:



This is regarded as due to the nature of the hydrogen bond, the resonance hybrid derived from the extreme forms



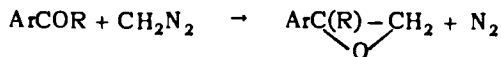
requiring the fixation of the remaining double bonds in the benzene ring.²³⁶

Chelate compounds exhibit certain characteristics; they are more volatile than similar unchelate compounds; they tend to be non-polar and, in general, they fail to show the characteristic OH absorption in the infrared region.

An indication of chelation in 4-o-acetylresacetophenone is the inability of this compound to give the expected 4,6-diacetyl derivative, yielding instead the 2,4-diacetyl compound. In the Claisen rearrangement of the 4-allyl ether of resacetophenone, the allyl group migrates to the 2-position and not to the 6-position.²³⁷

Miscellaneous Reactions

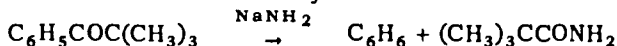
Aromatic ketones reacting with diazomethane are partially converted into epoxides:²³⁸



Migration of the phenyl group takes place simultaneously to give an aralkyl-alkyl ketone, which on further reaction with diazomethane gives an epoxide.

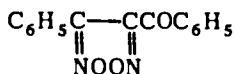
Ortho ethers of acetophenone, $\text{C}_6\text{H}_5\text{C(OR)}_2\text{CH}_3$, have been obtained through the reaction of acetophenone with *ortho* esters of formic acid.²³⁹ When heated under atmospheric pressure or, preferably, with acid chlorides or pyridine, such *ortho* ethers lose alcohol and give alkyl ethers of phenyl olefinic alcohols.²⁴⁰

When trialkyl acetophenones in benzene solution are heated with sodamide, they decompose into benzene and trialkyl acetamides.²⁴¹



Ketones of the type of 3,4-diphenylbenzophenone, $(\text{C}_6\text{H}_5)_2\text{C}_6\text{H}_3\text{COC}_6\text{H}_5$, can also be cleaved with sodium amide.²⁴²

The alkyl groups in aryl aliphatic ketones, ArCOAlk , are more reactive than the aryl groups and are attacked preferentially by halogens and nitric acid. Thus, the halogenation of acetophenone gives the compounds $\text{C}_6\text{H}_5\text{COCH}_2\text{X}$, $\text{C}_6\text{H}_5\text{COCHX}_2$, and $\text{C}_6\text{H}_5\text{COCX}_3$;²⁴³ with nitric acid of sp. g. 1.4, "diphenyl-dinitrosacyl",



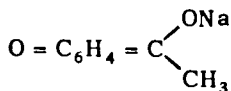
is the principal product.²⁴⁴

Aryl methyl ketones form crystalline compounds with phosphoric and arsenic esters; these are decomposed by heat to aromatic hydrocarbons with cleavage of the carbonyl group.²⁴⁵

Mixed aryl aliphatic ketones are converted to sulfonic acids when heated with sulfuric acid.²⁴⁶

Aryl- β -diketones, like aliphatic β -diketones, dissolve in aqueous alkalis, a property which distinguishes them from other diketones.

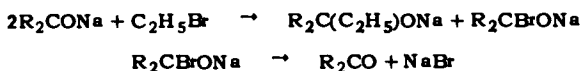
o-Hydroxy ketones form two series of salts; the normal, colorless phenolates, such as $\text{CH}_3\text{COC}_6\text{H}_4\text{ONa}$, and colored quinoid salts, such as



Aromatic ketones react with alkali metals to form *ketyls*,²⁴⁷ RR'COM . These are monomeric bodies in which the carbonyl carbon atom is tervalent. Metal ketyls are paramagnetic bodies. ω -Diethyltrimethyl-, ω -dimethylethyl-, ω -methyldiethyl-, and ω -triethyl-acetophenone give stable crystalline ketyls.

While the ability to form ketyls had been regarded as a characteristic of aromatic ketones, it has been demonstrated that ketyls may be obtained also from aliphatic ketones.²⁴⁸ Di-*tert*-butyl ketone, for example, reacts with sodium to form a deep-red ketyl, the solution of which is decolorized on exposure to air, with the formation of hydrogen peroxide. Isopropyl *tert*-butyl ketone likewise gives a ketyl.

Metal ketyls apparently react with alkyl halides to form the sodio derivative of an alkylated alcohol.¹¹⁸



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CHAPTER 25

AROMATIC CARBOXYLIC ACIDS AND RELATED COMPOUNDS

AROMATIC CARBOXYLIC ACIDS

Methods of Preparation

Aromatic carboxylic acids may be prepared from homologs of benzene through the oxidation of a side chain. Suitable oxidizing agents are chromic acid, dilute nitric acid, potassium permanganate, and potassium ferricyanide.

Oxidation with *chromic acid* is carried out by use of a mixture of chromic acid and glacial acetic acid, or one of 3 parts potassium chromate and 1 part 30 to 50% sulfuric acid. Among hydrocarbons with two substituents, only the *para* and *meta* isomers are oxidized to acids; *ortho* compounds either remain unattacked, or are completely destroyed. Negative groups in *ortho* position with respect to an alkyl group protect the latter.¹

When *nitric acid* is used for the purpose of oxidizing a side chain, the amount of nitrated product formed is kept down to a minimum by diluting the acid with 3 volumes of water. Oxidation is effected by boiling the mixture of the diluted acid and the hydrocarbon for some time. The nitrated acids formed in the course of the reaction are reduced to amino acids with tin and concentrated hydrochloric acid and remain in solution in the acid, and thereby are separated readily from the unnitrated acids formed. If the aromatic compound contains more than one alkyl group, the higher alkyl group is attacked first by both nitric and chromic acids.

Potassium permanganate generally effects the oxidation of the side chain at room temperature;² *ortho* disubstituted derivatives may be oxidized in certain instances without the disruption of the aromatic ring.

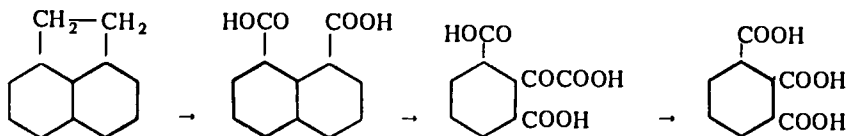
Potassium ferricyanide causes the oxidation of a methyl group to carboxyl if there is a nitro group in the *ortho* position to the methyl group; oxidation does not take place if the nitro group is in the *meta* position.³

Aromatic carboxylic acids may be obtained also through the oxidation of a ring in polycyclic hydrocarbons. Phthalic acid may be produced, for example, through the oxidation of naphthalene with nitric acid or with potassium permanganate.⁴ Phthalic anhydride is made on the commercial scale through the catalytic oxidation of vapors of naphthalene with air in the presence of vanadium oxide.

One process utilizes as a catalyst pumice of 3 mm size impregnated with a hot concentrated solution of ammonium vanadate and dried. The granules are heated at 400° until they assume a reddish brown color. The naphthalene is heated to 110° and moist air passed over it to carry over the vapors of naphthalene, and the mixture of air and naphthalene is passed through the catalyst bed heated at 450°. A 90 to 95% yield has been

achieved by use of a catalyst tube 5 cc in dia. and 10 cm long, and passing through 200 lit of air per hour charged with 5 gm of naphthalene vapors.²³⁰

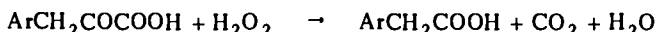
Oxidation of other polynuclear compounds such as anthracene and indene, also yields dicarboxylic acids.⁵ Helmintic acid has been made through the oxidation of acenaphthene.⁶



This compound can also be obtained by oxidizing naphthoic acid.

Aromatic acids may be prepared through the oxidation of aromatic alcohols or aldehydes. They may be made further through the oxidation of aromatic compounds containing halomethyl groups attached to the nucleus. Terephthalic acid is best prepared by oxidizing *p*-xylylene dibromide with alkaline permanganate.⁷ This compound is also obtained from *p*-toluic acid by oxidation with the same reagent.

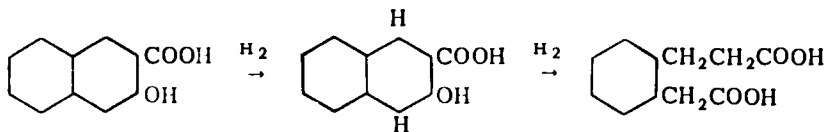
Aromatically substituted pyruvic acids, which may be prepared through the condensation of aromatic aldehydes with hippuric acid, are oxidized to aryl acetic acids by hydrogen peroxide:⁸



Certain naphthalene derivatives yield dicarboxylic acids on oxidation. β -Naphthol, for example, gives *o*-carboxycinnamic acid when treated with potassium permanganate; *o*-carboxyhydrocinnamic acid,



results through the oxidation of tetrahydro- β -naphthylamine with potassium permanganate. Reduction of 3-hydroxy- β -naphthoic acid to its dihydroderivative followed by hydrolysis results in the formation of *o*-(β -carboxyethyl)phenylacetic acid:

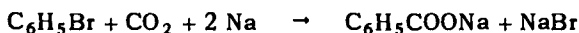


This acid is also obtained in the form of its sodium salt by heating β -hydroxy-naphthoic acid with sodium and amyl alcohol.

o-Cyanocinnamic acid, $\text{CNC}_6\text{H}_4\text{CH}=\text{CHCOOH}$, is obtained in the form of its sodium salt by heating α -nitroso- β -naphthol sodium to 250°.⁹

Nuclear Syntheses

A carboxyl group may be introduced into an aromatic nucleus through the reaction of an aromatic bromide with carbon dioxide in the presence of metallic sodium:¹⁰



The procedure is to dissolve the halide in a large amount of benzene or xylene, to add one and a half times the calculated quantity of sodium in the form of thin shavings, and to pass moist carbon dioxide through the liquid heated on a boiling water bath for one or two days. The yields are generally quite low. Yields may be greatly improved by heating the mixture with carbon dioxide in an autoclave. Diphenyls and diketones are formed as by-products. Dihalo compounds and benzyl chloride do not undergo the reaction.

Aromatic carboxylic acids may be prepared by the Wurtz reaction; namely, through the action of sodium on a mixture of bromobenzene and ethyl chloro-carbonate.

The reaction of carbon dioxide with aryl magnesium halides leads to the formation of aromatic carboxylic acids.

Aromatic carboxylic acids are formed through the reaction of carbon dioxide with aromatic hydrocarbons under high pressure and at high temperatures in the presence of aluminum chloride.¹¹ They are formed also through the reaction of carbon monoxide and steam with chlorinated aromatic hydrocarbons under pressure at 300° in the presence of catalysts.¹²

An important method of preparation of aromatic carboxylic acids is by way of the nitriles of the acids, which may be obtained either through the replacement of halogens or sulfonic groups with the cyano group, or through the Sandmeyer's diazo reaction.

The subject of the hydrolysis of nitriles has been taken up in Chapter 9 dealing with aliphatic nitriles. Hydrolysis of aromatic nitriles may be accomplished by the methods employed for aliphatic nitriles. Disubstituted nitriles in which the substituents are in the *ortho* position with respect to the cyano group are hydrolyzed with difficulty.¹³ Hydrolysis of such nitriles has been accomplished by prolonged heating with alcoholic potassium hydroxide. Hydrolysis of these nitriles with concentrated sulfuric acid may lead to the formation of the corresponding amide rather than the acid. The presence of a negative group in an aromatic nitrile facilitates the hydrolysis of the nitriles.¹⁴ The position of the nitro group in the ring determines its effect on the reactivity of the cyano group.¹⁵

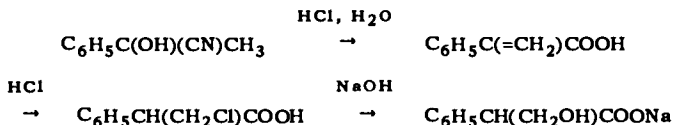
Acids cause the removal of the cyano group from cyanoacridines, and it is necessary to hydrolyze these compounds by heating with alkalis. Hydrolysis may be effected by heating with caustic in a sealed tube at 160 to 170°.¹⁶

Sulfuric acid causes the hydration of the triple bond in phenylpropionic nitrile, $\text{C}_6\text{H}_5\text{C} \equiv \text{CCN}$. Alcoholic potassium hydroxide reacts vigorously with acetylenic nitriles forming both acetylenic acids and compounds of the type $\text{RC}(\text{OC}_2\text{H}_5) = \text{CHCN}$, which are subsequently hydrolyzed to the corresponding acids.¹⁷

Hydrolysis of nitriles that are insoluble in sulfuric acid may often be accomplished by use of a mixture of sulfuric and acetic acids.¹⁸ Occasionally the yield of acid may be improved by first converting the nitrile to the corresponding amide and then hydrolyzing this.¹⁹ Certain very stable nitriles may be saponified by fusion with alkali; thus, pyrene cyanide gives by this treatment the alkali metal salt of pyrenecarboxylic acid.²⁰

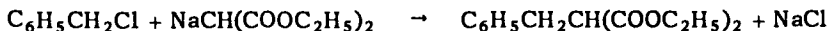
Hydrolysis of some cyanohydrins presents complications. Thus, while cinnamaldehyde cyanohydrin, $\text{C}_6\text{H}_5\text{CH} = \text{CHCH}(\text{OH})\text{CN}$, may be converted by cold hydrochloric acid to phenyl- α -hydroxycrotonamide from which by careful hydrolysis phenyl- α -hydroxycrotonic acid may be obtained, hydrolysis of the cyanohydrin under drastic conditions leads to the formation of γ -benzoylpropionic acid, $\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{COOH}$.²¹ Acetophenone cyanohydrin may be hydrolyzed with cold concentrated hydrochloric acid to atrolactic acid;

but hydrolysis with boiling concentrated hydrochloric acid, followed by treatment with sodium hydroxide gives the sodium salt of tropic, or α -phenyl- β -hydroxypropionic acid:



When benzoyl cyanide is hydrolyzed with boiling concentrated hydrochloric acid, benzoic acid is formed; if however, the nitrile is allowed to react with hydrochloric acid at room temperature and then the product is heated for a short period at 70°, phenylglyoxylic acid, $\text{C}_6\text{H}_5\text{COCO}_2\text{H}$, is obtained.²²

The introduction of a group containing one or more carboxyl groups in an aromatic molecule may be effected through the reaction of an aryl alkyl halide with the sodio derivative of a compound containing at least one esterified carboxyl group and an active methylene:²³



Carbon to carbon union may be brought about by the action of metallic sodium on the benzyl esters of aliphatic acids through the elimination of one molecule of acid.²⁴ Thus, benzyl acetate yields benzyl phenylpropionate:



Unsaturated acids are also formed in the reaction as by-products:



Carboxylic Acids with Other Functional Groups

Phenol and Alcohol Carboxylic Acids

The general methods of formation of phenols are applicable to aromatic compounds containing carboxyl groups. Thus phenolic acids may be prepared from amino acids via the diazo acids and the replacement of the diazo group by hydroxyl;²⁵ they may be obtained from sulfo- and halobenzoic acids by fusion with alkalis. 4,6-Dibromoisophthalic acid is converted to 4,6-dihydroxyisophthalic acid by boiling with an aqueous solution containing the acetates of sodium and copper.²⁶ Oxidation of the ammonium salts of acids of the benzoic series with hydrogen peroxide gives rise to *o*-, *m*-, and *p*-hydroxybenzoic acids.²⁷

Homologs of phenol containing nuclear methyl groups are oxidized to phenol carboxylic acids when fused with alkalis; phenolic aldehydes are also oxidized to carboxylic acids by fusion with alkalis. Sulfuric and phosphoric esters of homologs of phenol may be oxidized to carboxylic esters, and these may be hydrolyzed to the corresponding phenol carboxylic acids.

The oxidation of salicylic acid with potassium persulfate leads to the formation of 2,5-dihydroxybenzoic acid (gentisic acid).²⁸

Since the oxidation of aldehydes leads to the formation of acids, *Gattermann's method*, considered in connection with aromatic carbonyl compounds, may serve

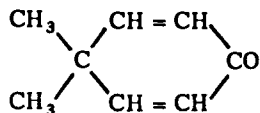
as the basis for the formation of carboxylic acids derived from phenol ethers. Orcellinic acid has been obtained by this method from orcinol, oxidation of the aldehyde having been carried out with potassium permanganate in acetone solution.

Reimer-Tiemann's Reaction

Phenol carboxylic acids are formed when phenols are boiled with a mixture of carbon tetrachloride and potassium hydroxide, preferably in the presence of metallic copper or copper compounds:²⁹

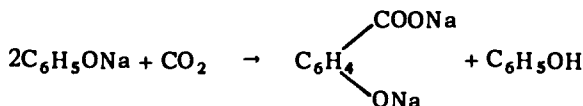


In most cases the carboxyl group enters the *para* position relatively to the hydroxyl group, but a small amount of the *ortho* compound is invariably formed. The reaction is of wide applicability and has been employed for the introduction of a carboxyl group into nitro and chlorophenols. *Para* alkylated phenols yield derivatives of ketodihydrobenzenes, such as



Kolbe-Schmitt Reaction³⁰

When dry sodium phenolate is heated at 180-200° in a current of carbon dioxide one half of the phenol becomes converted to disodium salicylate:



The reaction may be carried out in two stages, first conducting carbon dioxide over sodium phenolate to form sodium phenyl carbonate, $\text{C}_6\text{H}_5\text{OCOONa}$, and then heating this at 120 to 130°, whereupon the compound becomes converted to sodium salicylate. It is not necessary to prepare the sodium phenolate; the reaction may be carried out by mixing phenol intimately with an excess of sodium hydroxide and heating the mixture in an autoclave with carbon dioxide under pressure at 120 to 140°.³¹ All of the phenol is converted to the phenolic acid by this method. Sodium salicylate may be obtained in almost quantitative yield, for example, by heating a mixture of sodium hydroxide with 7 to 8 parts of phenol until all water is distilled and then conducting carbon dioxide through the melt while the temperature is gradually lowered to 90°. The temperature is maintained at this point for 15 hours in order to complete the reaction.

The carboxyl group enters the *ortho* position with respect to the hydroxyl group. If the temperature is allowed to exceed 140°, some *para* compound also forms. Potassium phenolate gives potassium salicylate at 150°, but at higher temperatures an increasing proportion of *p*-hydroxybenzoate is formed, and at 220° the *para* compound becomes the sole product.

The reaction takes place very readily with polyhydric phenols, and especially readily when the hydroxyl groups are situated in meta position, as is the case with resorcinol or phloroglucinol. These compounds can be converted to carboxylic acids by heating with fairly concentrated aqueous solutions of ammonium or alkali bicarbonates at 130°, preferably in a stream of carbon dioxide.³² When working with sensitive phenols it is desirable to add some potassium bisulfite to the reaction mixture. The acids may be prepared conveniently by heating the phenol with ammonium carbonate in an autoclave at 140°. The carboxyl group enters the *ortho* or *para* position with respect to one hydroxyl group, but never in *meta* position with respect to both hydroxyl groups. Several isomers are often formed simultaneously. Pyrocatechol gives principally 3,4-dihydroxybenzoic acid,³³ with some 2,3-dihydroxybenzoic acid (pyrocatechol *o*-carboxylic acid). Resorcinol gives 2,4-dihydroxybenzoic acid (resorcylic acid),³⁴ with some 2,6-dihydroxybenzoic acid. Pyrogallol gives 2,3,4-trihydroxybenzoic acid, while phloroglucinol yields 2,4,6-trihydroxybenzoic acid.³⁴ Dicarboxylic acids may be obtained by this method by the repeated application of the reaction.

Naphthols also undergo the Kolbe-Schmitt reaction. A satisfactory procedure is to heat the sodium compound of the naphthol with carbon dioxide under pressure, or to heat a toluene solution of the naphthol with sodium and carbon dioxide. All water must be painstakingly eliminated from the reaction mixture. When β -naphthol is heated in this manner at 120 to 145°, 2,1-naphtholcarboxylic acid is obtained. If the mixture is heated at 200 to 250°, then 2,3-naphtholcarboxylic acid is obtained.³⁵ It may be pointed out that 2-naphthol-1-carboxylic acid is unstable, and the carboxyl group may be easily replaced by a nitro or azo group, while the 2,3-acid is quite stable. The 2,6-isomer can also be obtained under the proper conditions.³⁶

Carboxylic acids have been obtained from 2- and 3-phenanthrols by Kolbe-Schmitt's Synthesis, the 2-compound giving the 2,3-carboxylic acid, and the 3-compound and the 3-hydroxy-2-carboxylic acid.³⁷

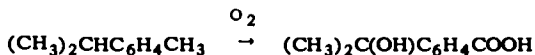
A carboxylic acid has also been obtained from α -hydroxy pyridine by the Kolbe-Schmitt method.³⁸

Alcohol Acids

Aromatic alcohol acids may be obtained through the partial reduction of keto acids; through the replacement of halogens in the side chain of aromatic halo acids with a hydroxyl group; from unsaturated acids by the usual methods employed for the introduction of hydroxyl groups in unsaturated compounds, such as by mild oxidation with potassium permanganate.³⁹ Alcohol acids may be obtained also by the hydrolysis of aromatic aldehyde or ketone cyanohydrins.⁴⁰ Thus, α -phenyllactic acid (atrolactic acid) is obtained from acetophenone cyanohydrin by boiling with dilute hydrochloric acid.

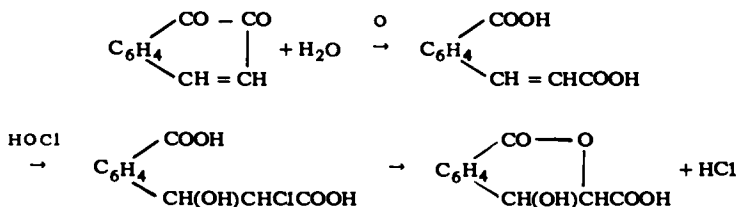
Ether acids are formed through the addition of alkoxy groups at the triple bond of acetylenic acids. Thus, β -methoxy- or β -ethoxycinnamic esters are formed by the addition of methyl or ethyl alcohol at the triple bond in ethyl phenylpropiolate under the action of sodium methoxide, or ethoxide.⁴¹ The phenoxy compound can also be obtained by this reaction.⁴²

Oxidation of *p*-cymene with potassium permanganate results in the formation of *p*-(hydroxyisopropyl)benzoic acid:⁴³



m-Cymene also undergoes a similar oxidation, giving the isomeric *m*-(hydroxyisopropyl)benzoic acid.

o-Carboxyphenylglyceric acid results when naphthoquinone is oxidized with hypochlorous acid:⁴⁴



Cinnamoyllactic ethyl ester, $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}_2\text{CH}(\text{OH})\text{COOC}_2\text{H}_5$, is obtained through the reaction of cinnamoyl chloride and ethyl lactate in the presence of pyridine.⁴⁵

Thiophenol Acids

Thiophenol acids may be prepared by the general methods employed for the preparation of aromatic mercaptans.

Thiosalicylic acid may be prepared from diazotized anthranilic acid by reaction with potassium xanthate and reduction of the resulting compound.⁴⁶ Alkali metal thiocyanates or sulfides may replace the xanthate in this reaction. Thiosalicylic acid may also be obtained by heating *o*-chlorobenzoic acid with alkali hydrogen sulfides in the presence of copper powder,⁴⁷ and by reduction of the unstable *o*-sulfobenzoic dichloride.

Thiophenolcarboxylic acid may also be obtained by the Kolbe-Schmitt method; i.e., by heating metallic derivatives of thiophenols with carbon dioxide under pressure.⁴⁸

Nitro and Amino Acids

Nitrated aromatic acids may be obtained through the reaction of nitric acid with aromatic carboxylic acids. Nitration of benzoic acid leads to the formation of metanitrobenzoic acid as the principal product with small amounts of the *ortho* and *para* isomers.⁴⁹

o-Nitrocinnamic acid is formed in 60% yield when cinnamic acid is added slowly to nitric acid of density 1.6.⁵⁰ The *para* isomer is formed simultaneously. The two isomers can be separated readily by shaking their ethyl esters with a limited amount of ethanol, whereby the *ortho* isomer is taken up quantitatively, the less soluble *para* nitro ester remaining largely behind.

Ethyl α,β -dinitrocinnamate is obtained when ethyl phenylpropiolate is subjected to the action of nitrogen peroxide at 0°.⁵¹

Phthalic acid yields on nitration 3- and 4-nitrophthalic acids.

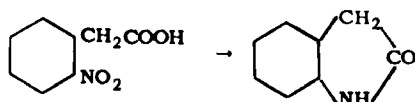
Nitration of 1-naphthoic acid leads to the formation of 5- and 8-nitro-1-naphthoic acids. On heating with nitric acid, these compounds give rise to 1,5- and 1,8-dinitronaphthalene. Nitration of 2-naphthoic acid gives 5- and 8-nitro-2-naphthoic acids.⁵²

Nitrated aromatic acids may be obtained through the oxidation of nitrated derivatives of homologs of benzene. Thus, *o*-nitrobenzoic acid is obtained from *o*-nitrotoluene by oxidation with potassium permanganate,⁵³ or with nitric acid vapors at 140°. The *meta* and *para* nitro acids are obtained by oxidizing *meta* and *para* nitrotoluenes with chromic acid mixture.⁵⁴ Such acids may be obtained also through the oxidation of nitrated derivatives of benzyl chloride: *o*- and *p*-nitrobenzoic acids are formed, for example, through the oxidation of *o*- and *p*-nitrobenzyl chloride with potassium permanganate.⁵⁵

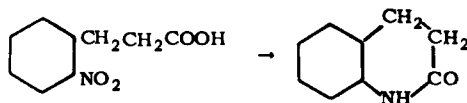
Nitrated benzoic acids are obtained from aromatic nitrated amines by conversion to nitrated nitriles and hydrolysis to the corresponding acids.

Aromatic amino acids are obtained from nitro carboxylic acids by reduction. Thus, aminocinnamic acids are formed from nitrocinnamic acids by reduction with tin and hydrochloric acid, or better, with ferrous sulfate in alkaline solution.⁵⁶ *o*-Aminophenylpropionic acid is formed similarly from *o*-nitrophenylpropionic acid by reduction with ferrous sulfate and ammonia.⁵⁷

Reduction of *o*-nitrophenylacetic acid with tin and hydrochloric acid results in the formation of *o*-aminophenylactam (oxindole):⁵⁸



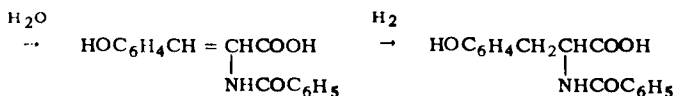
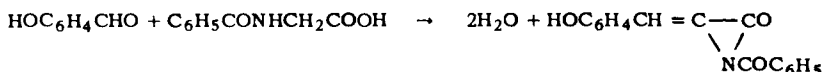
Reduction of *o*-nitrohydrocinnamic acid by the same method results in the formation of the lactam of aminohydrocinnamic acid (hydrocarbostyryl):⁵⁹

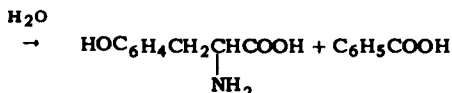


The hydroxy group in 2-hydroxy-3-naphthoic acid is replaceable with the amino group by reaction with ammonia.⁶⁰

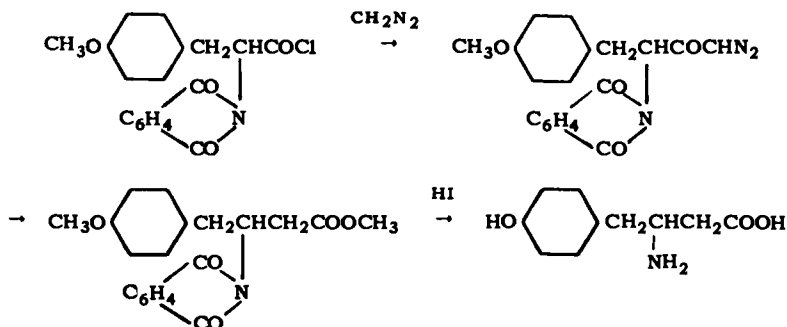
α -Aminocinnamic acid, $C_6H_5CH=C(NH_2)COOH$, in one isomeric form, is obtained as its amide by the reaction of ammonia with phenyldibromopropionic or α -bromocinnamic esters.⁶¹ It appears probable that this compound is in reality an imino acid derivative, $C_6H_5CH_2C(=NH)CONH_2$.

Tyrosine has been made through the condensation of *o*-hydroxybenzaldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate, followed by reduction of the unsaturated acid formed, and hydrolysis of the resulting saturated amido acid. The reactions involved in the preparation are indicated below:⁶²





Homologs of tyrosine have been prepared through the reaction of the chloride of O-methyl-N-phthalyl-1-tyrosine hydrate with diazaketone, conversion of the resulting diazoketone into the methyl ester of an acid with one more carbon atom by the Arndt-Eistert method, and finally boiling the phthalimide with hydrogen iodide to obtain a homolog of tyrosine:⁶³



Acetyl tyrosine chloride and the chlorides of other α -acyl amino acids fail to undergo this reaction. The reaction is applicable to the phthalimido derivatives of other α -amino acid chlorides.

Azoxybenzoic acids, such as $\text{HOCOC}_6\text{H}_4\text{NO} = \text{NC}_6\text{H}_4\text{COOH}$, are obtained by heating nitrobenzoic acids successively with alcoholic potassium hydroxide and alcoholic potassium cyanide.⁶⁴ They may also be obtained by treating o-azidobenzoic acids with sodium hydroxide.⁶⁵ o-Azoxybenzoic acid and p-azoxybenzoic acid are formed when o- and p-nitrobenzoic acids are reduced with zinc and alcoholic ammonium chloride solution.⁶⁶

Azobenzoic acids, such as $\text{HOCOC}_6\text{H}_4\text{N} = \text{NC}_6\text{H}_4\text{COOH}$, are obtained from nitrobenzoic acids by reduction with sodium amalgam, or with zinc dust and alcoholic sodium hydroxide, and from the nitrobenzaldehydes by the action of very concentrated caustic soda.⁶⁶

sym-Hydrazinobenzoic acids are obtained from azobenzoic acids by reduction with sodium amalgam, or with ferrous sulfate and sodium hydroxide. They are formed also through the reduction of nitrobenzoic acids or their esters with zinc dust and acetic acid.⁶⁷

Halo and Sulfonic Acids

Halo aromatic acids may be obtained by direct halogenation of the acids. The first halogen atom entering the nucleus goes in the meta position. They may be obtained also by oxidation of *p*- and *m*-halogenated toluenes with chromic acid, and from *o*-halo derivatives of benzene by oxidation with dilute nitric acid or potassium permanganate. The amino group in aromatic amino acids may be replaced with halogens via the diazo compound by the usual methods. Monohalo phthalic acids have been prepared by this method from diazotized phthalic esters;⁶⁸ these compounds cannot be obtained through the halogenation of phthalic acid. Direct bromination of the acid, for example, gives 4,5-dibromo-

phthalic acid. The hydroxy group in phenol carboxylic acids may be replaced with chlorine by the action of phosphorus pentachloride.

Aromatic carboxylic acids may be chloromethylated by the usual method. *p*-Chloromethylsalicylic acid has been obtained from salicylic acid by reaction with formaldehyde and hydrogen chloride.⁶⁹

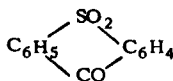
Sulfonated derivatives of aromatic acids may be obtained by the usual method of sulfonation, involving the reaction of fuming sulfuric acid at a high temperature. 3,5-Disulfobenzoic acid results when benzoic acid is heated with fuming sulfuric acid containing 70% sulfur trioxide, at 250° in a sealed tube. Cinnam-sulfonic acids have been prepared by the action of fuming sulfuric acid on cinnamic acid.⁷⁰ Sulfonation has been carried out also by use of vapors of sulfur trioxide. Benzoic acid sulfonated by this method yields largely the *m*-sulfo derivative together with a little of the *p*-isomer.⁷¹

Sulfur trioxide reacts with phthalic anhydride to form 4-sulfophthalic anhydride; 3,5-disulfophthalic anhydride forms if the reaction is carried out in the presence of mercuric salts. The sulfo group in these compounds may be replaced with chlorine by treatment with thionyl chloride or with a mixture of hydrochloric acid and sodium chlorate.⁷²

Sulfonated acids may be obtained by oxidizing sulfonated homologs of benzene. The three monosulfobenzoic acids have been prepared from toluene sulfonic acids by oxidation with potassium permanganate. Oxidation of *p*-toluene-sulfonamide with the same reagent leads to the formation of anhydrosulfonamino-benzoic acid (Saccharin).

Both *o*- and *p*-sulfobenzoic acids are formed when potassium *m*-nitrobenzenesulfonate is boiled with aqueous potassium cyanide.⁷³

Diphenylsulfone-*o*-carboxylic acid, $C_6H_5SO_2C_6H_4COOH$, may be obtained by heating the potassium salt of *o*-chlorobenzoic acid with benzenesulfonic acid in aqueous or amyl alcoholic solution in the presence of copper. The compound is converted into benzophenone sulfone,



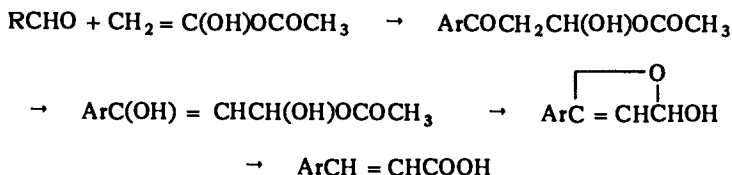
under the action of concentrated sulfuric acid.⁷⁴

Olefin Carboxylic Acids

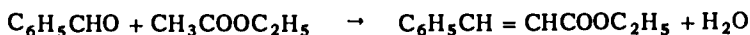
Aromatic olefin carboxylic acids may be obtained from aromatic acids containing aliphatic side chains by the general methods employed for the preparation of aliphatic olefin compounds. Among such methods are dehydration of hydroxy acids, dehydrohalogenation of halo derivatives, pyrolysis of acylated derivatives of hydroxy acids, etc.

A method of considerable importance, primarily applicable to aromatic compounds, utilizes the reaction of aromatic aldehydes with the anhydride of an aliphatic acid in the presence of the sodium salt of the acid. This method of wide applicability, known as *Perkin's synthesis*,⁷⁵ has been considered in

Chapter 5 dealing with reactions of carbonyl compounds. In the reaction, the α -carbon atom of the acid combines with the carbon atom of the aldehyde group. The reaction apparently proceeds in stages: the acid anhydride probably enolizes and the aldehyde reacts with the enol to form an addition product; the latter in turn enolizes and forms an inner hydroxy ether which rearranges to the olefinic acid:⁷⁶



Claisen's condensation, also dealt with in Chapter 5, yields unsaturated aromatic acids.⁷⁷ It involves the reaction of aromatic aldehydes with aliphatic esters in the presence of metallic sodium or sodium ethoxide:



Another method, also previously considered in Chapter 5, namely the *Knoevenagel condensation*, utilizes the reaction of aldehydes with carboxylic acids containing a reactive methylene, in the presence of ammonia or other nitrogen bases.⁷⁸ An anil of the aldehyde $\text{RCH} = \text{NR}'$ is apparently formed as an intermediate in the reaction. Aldehydes like gallaldehyde, which yield stable initial addition compounds with the base incapable of losing water under the conditions of the synthesis, do not undergo the reaction. Styrylacetic acid,



results from phenylacetaldehyde and malonic acid by warming in the presence of pyridine.⁷⁹ Phenylethylidenemalonic acid is the first product formed; partial decarboxylation and migration of the double bond then follows with the formation of the 2,3-unsaturated acid.

α -Acetaminocinnamic azlactone, $\text{C}_6\text{H}_5\text{CH} = \text{CN} = \text{C}(\text{CH}_3)\text{OCO}$, is obtained from benzaldehyde and hippuric acid under the action of sodium acetate and acetic anhydride.⁸⁰

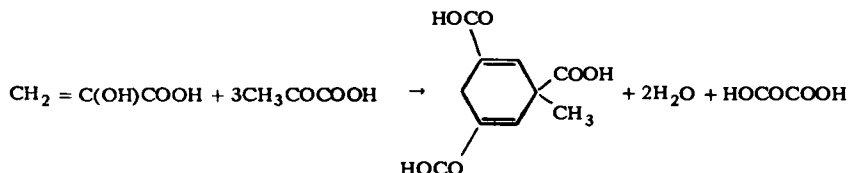
Cinnamic acid has been obtained by heating benzylidene chloride with sodium acetate, and by oxidizing benzylidene acetone with sodium hypochlorite.⁸¹ The phenyl ester of the acid results when phenyl fumarate is heated.

α -Iodocinnamic acid, $\text{C}_6\text{H}_5\text{CH} = \text{CICOOH}$, is obtained from phenylpyruvic acid by the action of iodine and potassium iodide in caustic solution.⁸²

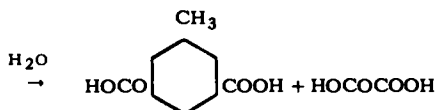
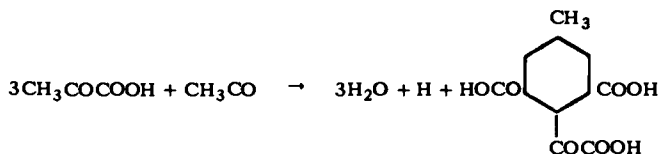
Syntheses from Aliphatic Compounds, Involving Ring Closure

Many aromatic carboxylic acids have been obtained from aliphatic compounds by ring closure. Pyruvic, acetoacetic, malonic, and acetonedicarboxylic acids or their derivatives have been used in such syntheses.

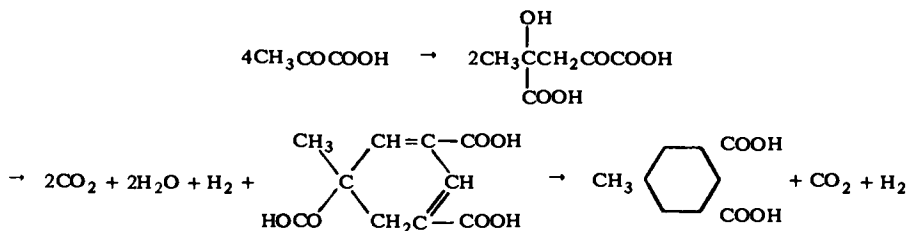
1-Methyl-1,2-dihydrotrimesic acid has been obtained through the condensation of four molecules of pyruvic acid:⁸³



Uvitic acid has been made through the condensation of pyruvic acid with acet-aldehyde:⁸⁴

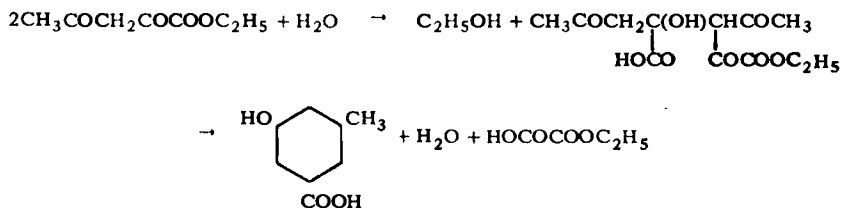


5-Methylisophthalic acid has been synthesized from pyruvic acid by boiling with baryta water or sodium hydroxide solution:⁸⁵

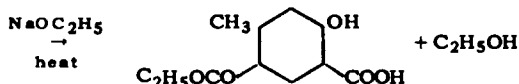
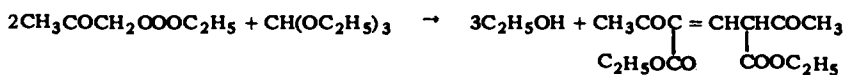


The final decarboxylation step may be effected by prolonged boiling with baryta water, but a better procedure is to heat the original product of condensation with concentrated sulfuric acid. When a mixture of pyruvic acid and propyl aldehyde or isobutyl aldehyde is used in this synthesis, 5-ethylisophthalic and 5-isopropylisophthalic acids are formed respectively.⁸⁶

1,3,5-Hydroxyvitolic acid has been prepared by gradually decomposing the sodio derivative of acetopyruvic ester with water, and then heating the resulting product with an excess of baryta water:



m-Hydroxyvitolic acid⁸⁷ has been obtained through the reaction of acetoacetic ester with orthoformic ester:



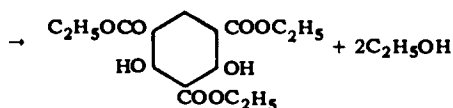
2,5-Dihydroxyterephthalic diethyl ester 1a formed by the action of sodium ethoxide on dibromoacetoacetic ester.⁸⁸

Hydroxyuvitic acid is formed by the reaction of chloroform, chloral, or ethyl trichloroacetate with sodio acetoacetic ester.⁸⁹ Methenyl bis-acetoacetic ester is probably an intermediate product in this reaction.

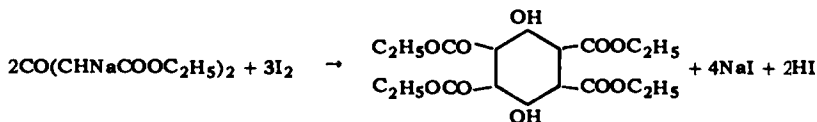
Hydroxymethyltrimesic and dihydroxytrimesic esters have been obtained through the condensation of ethoxyacetoacetic ester with ethoxymalonic ester and with sodio acetonedicarboxylic ester respectively.⁹⁰

Phloroglucinoldicarboxylic ester has been made by the condensation of three molecules of sodio malonic ester.

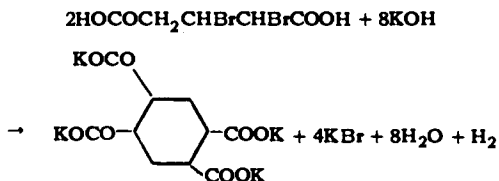
Dihydroxytrimesic triethyl ester has been prepared through the condensation of ethoxymethylenemalonic ester with acetone dicarboxylic ester in the presence of sodium ethoxide.⁹¹



Hydroquinone tetracarboxylic ester has been obtained by the action of iodine on sodio acetonedicarboxylic ester.⁹²



Pyromellitic acid results in the form of its potassium salt when α,β -dibromoglutaric acid is heated with potassium hydroxide solution:⁹³



Behavior and Reactions of Aromatic Carboxylic Acids

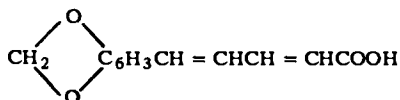
Most aromatic carboxylic acids are difficultly soluble in cold water. They may be *decarboxylated* by heating with lime or, preferably, soda lime. Polycarboxylic acids give acids with fewer carboxyl groups as intermediate compounds. Decarboxylation may be brought about also by heating with concentrated hydriodic acid or with phosphonium iodide.

The strength of aromatic carboxylic acids is greatly influenced by substituents in the ring. Hydroxyl groups in the *ortho* position increase acid strength; the effect of two *ortho* hydroxyl groups is especially great. The dissociation constants of a number of aromatic acids is given below:

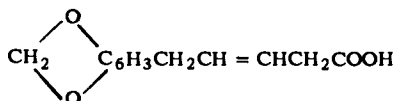
	<i>K</i>		<i>K</i>
benzoic acid	0.006	phloroglucinolcarboxylic acid	2.1
<i>o</i> -hydroxybenzoic acid	0.102	phenylacetic acid	0.0056
<i>m</i> - " "	0.087	hydrocinnamic acid	0.0023
<i>p</i> - " "	0.003	<i>o</i> -phthalic acid	0.121
2,6-dihydroxybenzoic acid	5.0	isophthalic acid	0.029
pyrogallolcarboxylic acid	0.55		

Aromatic carboxylic acids show a particularly great susceptibility to reduction. Benzoic acid is converted to hexahydrobenzoic acid by reduction with sodium amalgam in alkaline solution in an atmosphere of carbon dioxide.⁹⁴ Dicarboxylic acids are reduced more readily than monocarboxylic acids.

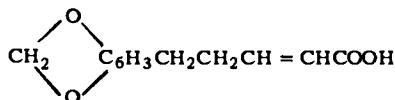
When piperic acid,



is reduced with sodium amalgam at a low temperature and in the absence of any large excess of alkali, α -dihydropiperic acid,

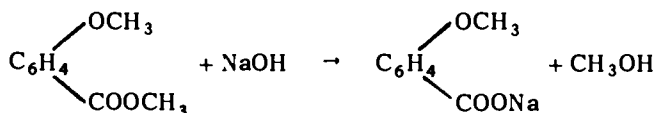


is obtained. On the other hand, when reduction is effected in strongly alkaline solution, the β -acid,



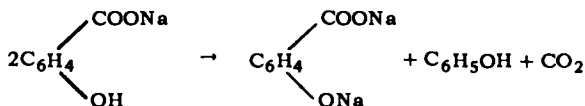
is obtained. The α -acid adds bromine at the double bond giving a dibromo derivative, while the β -acid gives substitution products, the halogen entering the aromatic ring. The α -acid may be converted to the β -acid by heating with sodium hydroxide solution.

Phenol monocarboxylic acids react as monobasic acids; on reaction with sodium carbonate only the carboxylic hydrogen is replaced with sodium. Sodium hydroxide, on the other hand, reacts with both the phenolic and carboxylic hydroxyl groups, replacing the hydrogen in both with sodium. When the resulting phenolic salts are subjected to the action of carbon dioxide, the phenolic hydroxyl group is regenerated. Disodium salicylate, for example, gives sodium salicylate, $\text{HOC}_6\text{H}_4\text{COONa}$, when treated with carbon dioxide. Ether-esters of phenol carboxylic acids give on hydrolysis with sodium hydroxide the sodium salt of the ether acid, only the ester portion undergoing hydrolysis:



Ortho and *para* hydroxy carboxylic acid may be decarboxylated by heating alone or with aromatic bases, or with concentrated hydrochloric acid. *Meta* hydroxy carboxylic acids cannot be thus decarboxylated. All hydroxybenzoic acids are decarboxylated when heated with lime.

When primary sodium salicylate is heated to 220° , it is partially decarboxylated to phenol:



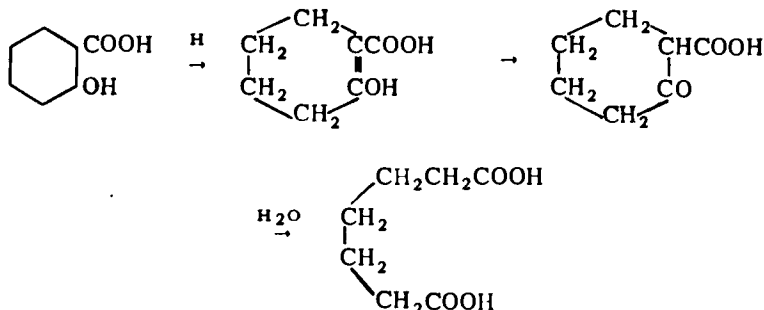
Monopotassium salicylate heated at 220° is similarly decarboxylated, but half of the compound is recovered as dipotassium *p*-hydroxybenzoate. Monosodium *p*-hydroxybenzoate heated at 280° gives disodium salicylate in addition to phenol and carbon dioxide.⁹⁵

Dihydroxybenzoic acids decompose on heating to the corresponding dihydric phenols and carbon dioxide.⁹⁶

2,1- β -Naphtholcarboxylic acid is converted to β -naphthol when heated alone or boiled with water. The loosening of the bond between the carboxyl group and the naphthyl group in this compound comes to evidence in other reactions. Thus, it is converted to nitroso- β -naphthol with nitrous acid. 2,3-Naphtholcarboxylic acid is very stable and resembles salicylic acid in its behavior.

Dihydroxycarboxylic acids in which the hydroxyl groups are in para position to one another are converted to quinones when heated with ferric chloride. Pseudocumene forms an exception and may be oxidized to pseudocumquinone carboxylic acid.⁹⁷

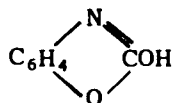
Aromatic *ortho* hydroxy carboxylic acids, reduced in alcoholic solution with sodium, are converted to dibasic acids of the pimelic series, probably through the intermediate formation of 1,3-keto acids:



Meta hydroxy acids, on the other hand, take up six atoms of hydrogen to form hydroxyhexamethylenecarboxylic acids.⁹⁸

Hydroxy carboxylic acids readily form polynuclear chains by loss of water. This tendency is especially marked in di- and trihydroxycarboxylic acids. The chlorides of these acids also give such compounds. These products are termed depsides and resemble tannins.

When azides of hydroxy acids are heated, the isocyanates first formed rearrange to cyclic compounds. Benzoxazolone,



is obtained, for example, from salicylazide.⁹⁹

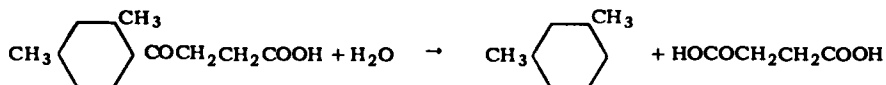
When β -benzylidene- α -hydroxypropionic acid is boiled with dilute hydrochloric acid, a migration of the oxygen atom from α to γ -position takes place, and the compound is converted almost quantitatively to the isomeric β -benzoylpropionic acid:



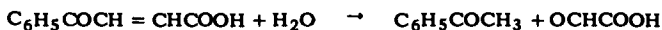
This behavior is also observed with other α , β -unsaturated α -hydroxy acids.

β -Benzoylpropionic acid, heated with acetic anhydride, or dry-distilled, loses the elements of water and gives phenyl- Δ^2 -crotonolactone.

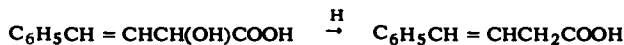
Aryl keto acids of the type $\text{ArCOCH}_2\text{CH}_2\text{COOH}$, in which alkyl substituents are present in the aromatic ring in the vicinity of the carbonyl group, undergo hydrolytic cleavage into an aromatic hydrocarbon and succinic acid when heated with hydrochloric acid:



β -Benzoylacrylic acids undergo hydrolytic cleavage into acetophenone and glyoxylic acid when heated with aqueous caustic:

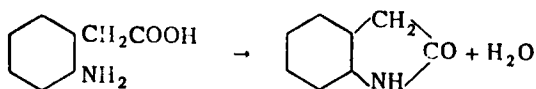


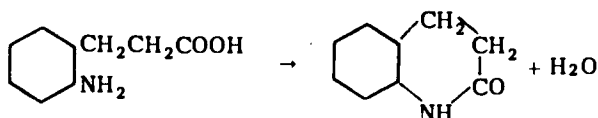
The behavior of β , γ -unsaturated α -hydroxy acids on reduction with sodium amalgam is characteristic: The hydroxyl group is eliminated and a β , γ -unsaturated acid results. β -Benzylidene propionic acid is thus obtained from β -benzylidene- α -hydroxypropionic acid:



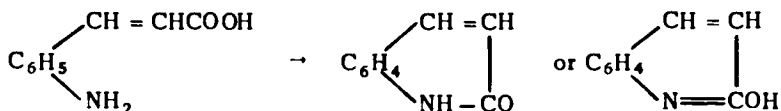
Aromatic amino carboxylic acids are amphoteric compounds forming salts both with alkalis and mineral acids. They do not, however, give salts with weak acids such as acetic acid.

Ortho amino derivatives of fatty aromatic acids in which the amino group stands in γ - or δ -position with respect to the carboxyl group are not stable but undergo ring closure, forming derivatives of indole or quinoline:





o-Amino cinnamic acid, unlike *o*-aminohydrocinnamic acid, is incapable of forming an anhydride. When heated with hydrochloric acid, carbostyryl is formed:¹⁰⁰



Halo acids with a reactive halogen are generally converted to the corresponding hydroxy acids when heated with aqueous sodium carbonate. β -Halocinnamic acid behaves exceptionally and is decomposed to styrene and carbon dioxide on treatment with aqueous sodium carbonate even in the cold.

AROMATIC ESTERS

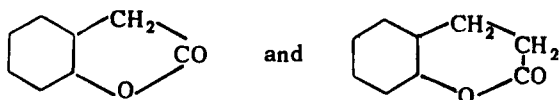
Methods of Formation

Esters of aromatic carboxylic acids may be prepared by the methods employed for the preparation of aliphatic esters. They may be obtained directly from the acid and alcohol by heating in the presence of hydrochloric acid; from the silver salts of the acids by reaction with alkyl halides, or by the action of dimethyl sulfate on the alkali metal salts of the acid. The methyl esters result on treating the free acid with diazomethane.¹⁰¹ Aromatic esters may be obtained also through the reaction of aromatic acyl halides with alcohols or alkali metal alcoholates, phenols, or phenolates. This reaction may be carried out by adding the chloride to a solution of the alcohol or phenol in pyridine; or by shaking the alkaline aqueous solution of the alcohol with the acyl chloride, with the progressive addition of the base until the mixture reacts permanently alkaline.¹⁰² All the hydroxyl groups in polyhydric alcohols, such as glucose, have been successfully benzoylated by this method.¹⁰³ Aromatic esters are also formed by passing a mixture of the vapors of the acid and alcohol over thorium oxide heated to 400°.¹⁰⁴ Dicarboxylic acids are partially decarboxylated by this treatment and yield esters of monocarboxylic acids.¹⁰⁵

In the direct esterification of aromatic acids, *ortho* substituted acids, such as mesitylene carboxylic acid, 2,6-dibromo-, 2,4,6-tribromo-, and 2,4,6-trinitrobenzoic acid, react very slowly.¹⁰⁶ The effect of the methyl and hydroxyl groups in the *ortho* position is to diminish the reaction rate, while halogens and nitro groups in this position prevent ester formation completely at the usual temperatures at which esterification is carried out. Esterification can be effected successfully with *ortho* substituted acids at 180 to 200° even in the absence of a catalyst.

Phenylacetic acid is esterified much more readily than benzoic acid.

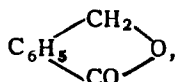
Inner ester or lactone formation has not been observed with phenol carboxylic acids in which the carboxyl group is directly attached to the phenyl group. On the other hand, acids in which the carboxyl group is removed from the aromatic radical by one or two carbon atoms readily form inner esters with an *ortho* hydroxy group. The simplest types of such inner esters are coumaranone and dihydrocoumarin,



derived from *o*-hydroxyphenylacetic and *o*-hydroxyphenylpropionic acids respectively. Inner ester formation of this type takes place also with aromatic hydroxy carboxylic acids in which the hydroxyl group is attached to a carbon atom joined to the aromatic nucleus, giving a phthalide.

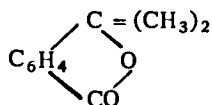
Phthalides

Phthalide,

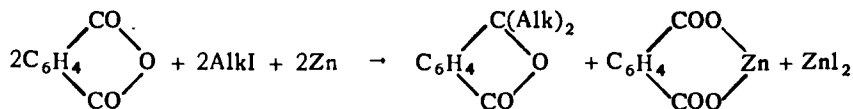


is most simply obtained through the reduction of phthalic anhydride with zinc dust and acetic acid, or catalytically over nickel at 200°. ¹⁰⁷ The compound may be made also by reducing phthalyl chloride with zinc and hydrochloric acid. ¹⁰⁸ Other methods of preparation involve the decomposition of nitrosophthalamidine with potassium hydroxide, ¹⁰⁹ and the reduction of phthalimide with zinc dust and aqueous caustic at room temperature. ¹¹⁰

The reaction of methylmagnesium iodide with phthalic anhydride results in the formation of dimethylphthalide, ¹¹¹

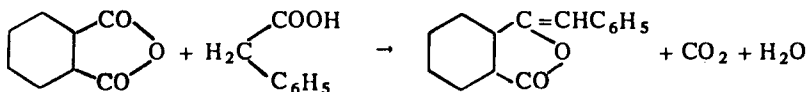


This compound and its homologs have been prepared through the reaction of methyl iodide and other alkyl iodides with phthalic anhydride in the presence of zinc dust: ²²⁹

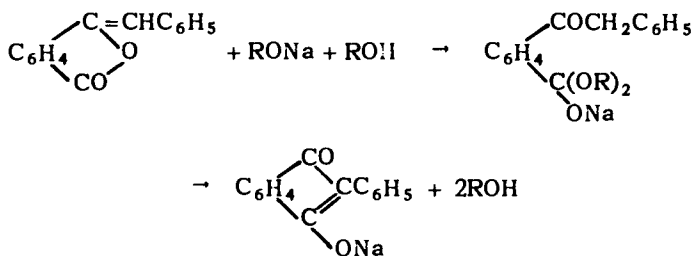


When propyl- or isopropyl iodide is used in this reaction, monopropyl- and mono-isopropylphthalides are obtained. Dimethylphthalide decomposes to sodium benzoate and acetone when heated with sodium hydroxide.

Phthalic anhydride reacts with phenylacetic acid to form benzalphthalide:¹¹²

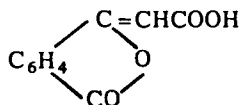


The reaction is carried out by heating phthalic anhydride with phenylacetic acid in the presence of a small quantity of anhydrous sodium acetate. The compound changes to phenylindandione under the influence of alcoholic sodium hydroxide.¹¹³

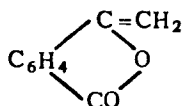


This rearrangement is referred to as the *Gabriel transformation*.

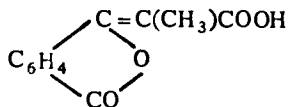
Phthalic anhydride is also capable of reacting with sodium acetate in the presence of acetic anhydride to give phthalylacetic acid,



which may be decarboxylated to methylenephthalide,¹¹⁴

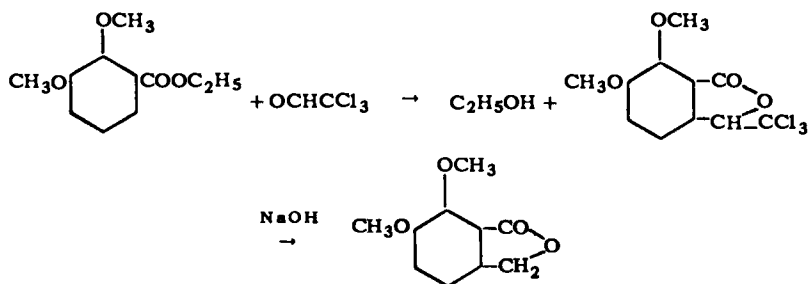


This compound is converted by alkalis to salts of acetophenone carboxylic acid. It may be brominated in chloroform solution to a dibromide. Other aliphatic acids also condense with phthalic anhydride in the manner of acetic acid, when a mixture of their sodium salt and anhydride with phthalic anhydride is heated. Thus, phthalylpropionic acid,



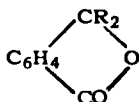
is obtained with propionic acid.¹¹⁵

Meconine, or 5,6-dimethoxyphthalide, has been synthesized from 2,3-dimethoxybenzoic ester and chloral, by decomposing the original condensation product by heating with caustic:¹¹⁶



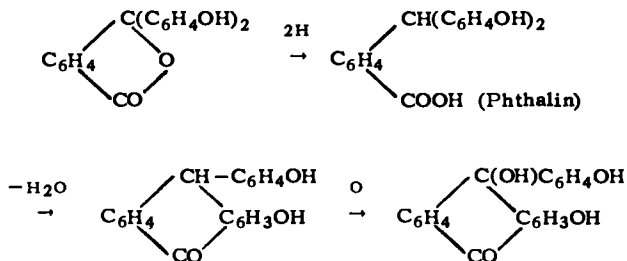
Phthaleins

Phthaleins are compounds of the type



derived from phthalic anhydride and phenols. They are formed when a mixture of phthalic anhydride and the phenol are heated in the presence of condensing agents, such as sulfuric acid and zinc chloride.¹¹⁷ The reaction is carried out by heating a mixture of 1 molecular proportion of the anhydride and 2 molecular proportions of the phenol with the condensing agent at 120°. Other agents used in the reaction are tin tetrachloride, aluminum chloride, boron trifluoride, phosphorus trichloride or oxychloride, and α - and β -naphthalenesulfonic acids. Reaction with polyhydric phenols proceeds in the absence of condensing agents, often by simply melting a mixture of the components. Di- and polyhydric phenols lose the elements of water and form an ether bridge between the two aryl groups entering the phthalein molecule.¹¹⁸ Fluorescein is an example of phthalein resulting from the reaction of a dihydric phenol, resorcinol, with phthalic anhydride.¹¹⁹

Phthaleins give phthalins on reduction; when treated with concentrated sulfuric acid, the latter are converted to phthalidines, and these give phthalideins on oxidation. These changes are indicated schematically below for the case of phenolphthalein:



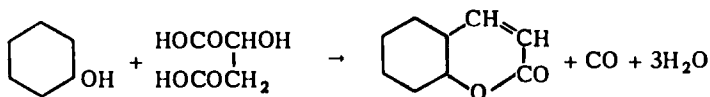
Conversion to phthalin can be effected by boiling phenolphthalein with zinc dust and aqueous caustic.

Phenolphthalein is cleaved to dihydroxybenzophenone and potassium benzoate when fused with potassium hydroxide.

Coumarins; Pechmann's Synthesis

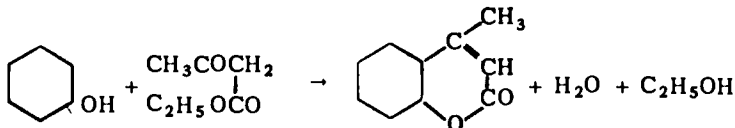
Coumarins are essentially inner esters of *cis*-*o*-hydroxycinnamic acids. The free acids are usually unstable and spontaneously change to their δ -lactones. The salts of the acids may be obtained readily by reaction of bases with coumarins, but when these salts are treated with a mineral acid, the free acid liberated loses the elements of water and the coumarin is regenerated. *o*-Nitrocoumarin forms an exception and may be converted to the free acid, which is stable in the dry condition, but gradually changes to the nitrocoumarin in contact with water or alcohol. Conversion of the acid to the coumarin takes place rapidly on heating.¹²⁰

A very general method of synthesis of coumarins, known as the Pechmann synthesis,¹²¹ involves the reaction of a phenol with malic acid:

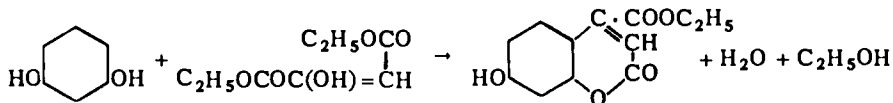


The semialdehyde of malonic acid, $\text{OCHCH}_2\text{COOH}$, is apparently first formed in this reaction, and condenses with the phenol to form the coumarin.

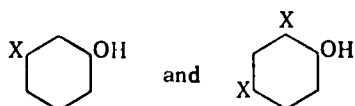
Acetoacetic ester reacts with phenols to form substituted coumarins:¹²²



Sulfuric acid or phosphorus pentoxide are used as condensing agents in the reaction. Homologs of acetoacetic ester may be employed in the reaction. Oxalacetic ester is capable of undergoing the reaction, giving β -carbethoxy coumarins:¹²³

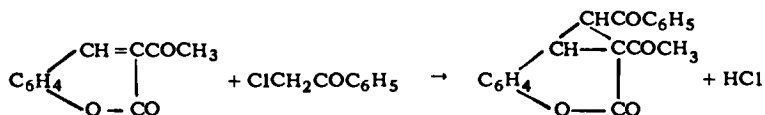


Phenol itself gives only a low yield of coumarin, but polyhydric phenols, especially phenols in which the hydroxyl groups are in meta position, react rather smoothly.¹²⁴ Resorcinol and *m*-cresol give good yields of coumarin, but *p*-cresol reacts with difficulty; *m*-diethylaminophenol reacts fairly readily but the ortho and para isomers react with greater difficulty. In general, phenols of the type

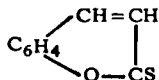


in which X is an alkyl, a hydroxyl, or a dialkylamino group, react readily giving good yields of coumarins.¹²⁵ Chlorine in these positions has a similar but less marked effect. Nitro, carboxyl, carbethoxy, and acyl groups, if present in the aromatic nucleus, inhibit the reaction. Quinol forms an exception and condenses well with oxalacetic ester. A nitro group in the 4-position in resorcinol inhibits the reaction more than one in the 2-position. An acyl group in the 4-position in resorcinol completely inhibits the reaction, while 2-acylresorcinols react readily.

Acetylcoumarin and other acyl coumarins condense with phenacyl halides to give tricyclic α -acyl- α β -phenacylidene coumarins:¹²⁶



Thiocoumarin,



results on fusing coumarin with phosphorus pentasulfide.¹²⁷ The compound is reconverted to coumarin on short boiling with alcoholic potassium hydroxide. Thiocoumarin reacts with hydroxylamine and phenylhydrazine to form coumaroxim and coumarphenylhydrazine respectively. These compounds cannot be obtained directly from coumarin.

AROMATIC ACID CHLORIDES AND ANHYDRIDES

Aromatic *acid halides* are prepared by the methods employed for the preparation of aliphatic acyl halides. One of the methods most commonly used for the preparation of acyl chlorides involves the reaction of the free acid with phosphorus pentachloride:



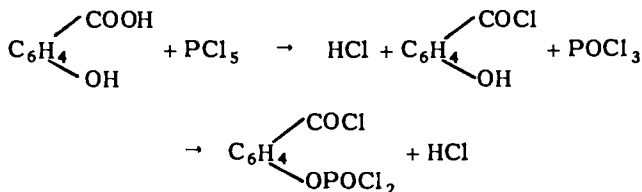
Benzoyl chloride may be obtained also by the action of chlorine on benzaldehyde.

In the preparation of chlorides of amino acids with phosphorus pentachloride, satisfactory results are obtained by using acetyl chloride as a diluent.

In cases where reaction with phosphorous pentachloride proceeds too vigorously, acetyl chloride may be used as a diluent to moderate the action of the reagent.

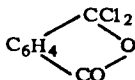
The chloride of trinitrobenzoic acid has been prepared by heating the acid with a mixture of phosphorus pentachloride and phosphorus oxychloride.²³¹

The reaction of phenol carboxylic acids with phosphorus pentachloride is complicated.¹²⁸ In general, the phosphorus oxychloride resulting from the reaction of the pentachloride with the carboxyl group reacts with the phenolic hydroxyl group to form an orthophosphoric ester chloride:



Ortho hydroxy acids having an *ortho* substituent, X, with respect to the hydroxyl group, $\text{C}_6\text{H}_3(\text{COOH})(\text{OH})\text{X}$, react normally to form the acid chloride, $\text{C}_6\text{H}_3(\text{COCl})(\text{OH})\text{X}$.

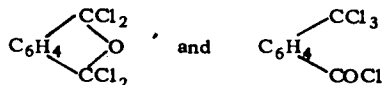
sym-Phthalyl chloride, $\text{C}_6\text{H}_4(\text{COCl})_2$, is formed through the action of phosphorus pentachloride on phthalic acid under atmospheric pressure at 150° . When the *sym*-chloride is heated with aluminum chloride on a water bath for some time, it is converted to the *asym*-chloride¹²⁹



The latter is reconverted to the symmetrical form when distilled.

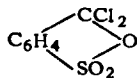
The symmetrical chloride reacts readily with alcohols to form phthalic esters. When reduced with sodium amalgam and acetic acid, it is converted to *o*-phthalyl alcohol. The symmetrical lactonic form is much less reactive.¹³⁰

o-Phthalylene tetrachlorides,

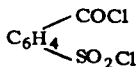


are formed by the action of phosphorus pentachloride on phthalyl chloride.¹³¹ *asym*-Tetrachlorophthalyl chloride is obtained from tetrachlorophthalic anhydride by heating it with phosphorus pentachloride in a sealed tube at 220° .¹³² It may be converted to the symmetrical form by heating

o-Sulfobenzoic acids give two chlorides when heated with phosphorus pentachloride: a stable form,



and an unstable form¹³³



Thionyl chloride has been employed for the preparation of acid chlorides. As a rule the anhydride is first formed, but on continued reaction with an excess of the reagent, the chloride of the acid is formed. Aromatic *p*-hydroxy acids react with thionyl chloride if there is a negative substituent in meta position to the carboxyl group. This specific action of thionyl chloride has manifested itself in other instances.²³²

It is important to free thionyl chloride from impurities, particularly from sulfur di-

oxide. This may be accomplished effectively by distilling the reagent after the addition of quinoline.²³³

The reaction of thionyl chloride with aromatic hydroxy acids generally results in the formation of inner anhydrides. Hydroxyisophthalic monomethyl ester gives a polymeric inner anhydride:²³⁴



Sulfonic chlorides may be employed effectively for the preparation of the chlorides of aromatic hydroxy acids. *Salicylic acid chloride* has been prepared by use of *p*-toluenesulfochloride in the following manner:

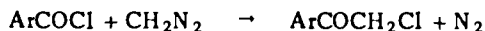
A mixture of a solution of 160 parts sodium salicylate in benzene with 190 parts *p*-toluenesulfonic chloride is heated under reflux until the latter disappears. The liquid is then filtered and concentrated by evaporation. The precipitate, consisting of a mixture of salicylide and solicyltoluenesulfonic ester, is filtered off and the residual benzene in the filtrate is evaporated off, leaving behind the oily salicylic acid chloride.

Aromatic acid chlorides may be obtained by Friedel-Crafts method, through the reaction of phosgene with an aromatic body in the presence of aluminum chloride.¹³⁴

The hydrolysis of aromatic acid chlorides proceeds with varying ease depending on the substituents in the ring.²³⁵ High rates of hydrolysis are observed when substituents are methyl or amino groups; chlorine causes a slight decrease in reactivity, while bromine produces a slight increase.

Aromatic acid chlorides react with hydroxy compounds to form esters of the corresponding acid, and with primary and secondary amines to form amides. The reaction is best carried out by Schotten-Baumann's method.¹³⁵ A satisfactory procedure is to mix the hydroxy compound or the amine and acyl chloride with water, and to add aqueous caustic to the mixture with good agitation until the liquid remains permanently alkaline. Sodium carbonate or sodium acetate may be used instead of caustic.

Aromatic acid chlorides generally react with diazomethane to form aryl ω -chloromethyl ketones:¹³⁶



Benzoyl chloride in ethereal solution gives but little chloroacetophenone; the principal product formed in this case is diazoacetophenone, $\text{C}_6\text{H}_5\text{COCHN}_2$.¹³⁷

The catalytic reduction of an acyl chloride leads to the formation of an alcohol, aldehyde, ester, or a hydrocarbon, depending on the conditions.¹³⁸

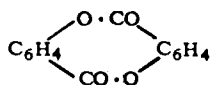
Benzoyl chloride has been converted to benzoyl iodide by heating with potassium iodide.²³⁶

Aromatic Anhydrides

Aromatic anhydrides result through the reaction of aromatic acid chlorides with the sodium or silver salt of the acid. They may be obtained also by heating

the chloride with baryta, or with anhydrous sodium carbonate in the presence of pyridine. Anhydrides have also been made by the action of lead nitrate or sodium nitrite on the chloride;¹³⁹ through the reaction of the chloride with potassium metabisulfite and tertiary bases;¹⁴⁰ and by heating the chloride with oxalic acid or oxalyl chloride.¹⁴¹ Benzoic anhydride has been made by heating benzotrichloride with anhydrous oxalic acid or concentrated sulfuric acid.¹⁴² Anhydrides may be obtained also by heating the acid with phosphorus oxychloride, or by the action of phosgene upon the acid in the presence of pyridine.

When salicylic acid in solution in toluene or xylene is made to react with phosphorus oxychloride, a tetrasalicylide and a polysalicylide are formed. The former is soluble in chloroform, while the latter does not dissolve in that solvent. A disalicylide,

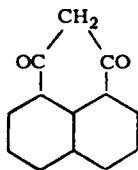


is formed through the reaction of phosgene and salicylic acid in pyridine solution.

Mixed anhydrides are formed through the reaction of an acid with the chloride or anhydride of another acid in the presence of pyridine or quinoline.¹⁴³

Aromatic *ortho* dicarboxylic acids such as phthalic acid are converted to their anhydride when they are heated.

1,8-Naphthalene dicarboxylic acid is converted to its anhydride on heating to 180°. This transformation takes place also when the acid is treated with alcoholic hydrochloric acid. The anhydride behaves like phthalic anhydride in many respects; it condenses with phenol to form phenolphthaleins.¹⁴⁴ On reaction with malonic ester in the presence of zinc chloride, it gives perinaphthoindandione.¹⁴⁵



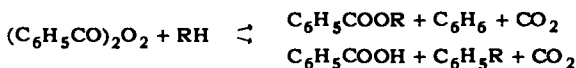
Acyl Peroxides

Aromatic acyl peroxides, $(\text{RCO})_2\text{O}_2$, may be prepared through the reaction of aromatic acid chlorides with the peroxides of barium or sodium and with hydrogen peroxide.¹⁴⁶ The compounds may be obtained through the acylation of hydrogen peroxide by the Schotten-Baumann method.

Some of the characteristic reactions of aromatic acyl peroxides may be illustrated by the behavior of benzoyl peroxide. Reaction with sodium ethoxide leads to the formation of ethyl benzoate and sodium perbenzoate:¹⁴⁷

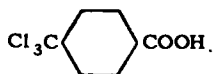


Perbenzoic acid may be freed from the perbenzoate by the action of dilute sulfuric acid, or even by carbon dioxide. Perbenzoic acid reacts with hydrocarbons to give an ester and benzene, or an acid and a hydrocarbon in the following manner:¹⁴⁸



Hydroxylated and carboxylated derivatives of hydrocarbons react similarly.

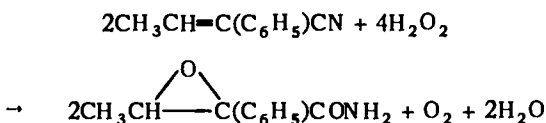
Benzoyl peroxide reacts with carbon tetrachloride forming ω -trichloro-*p*-toluic acid,¹⁴⁹



AROMATIC ACID AMIDES AND RELATED COMPOUNDS

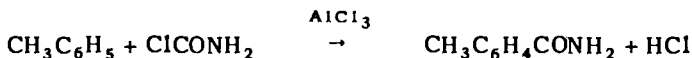
Amides

Aromatic acid amides may be prepared by the methods employed for the preparation of aliphatic amides. Partial hydrolysis of nitriles to amides, may generally be accomplished by use of cold concentrated hydrochloric or sulfuric acid. Mandelamide has been prepared by this method from mandelonitrile.¹⁵⁰ Phenyl α -hydroxycrotonic amide has been prepared from cinnamaldehyde cyanohydrin by use of a mixture of hydrochloric and sulfuric acid.¹⁵¹ Benzonitrile is converted to dibenzimidoxide, $(\text{C}_6\text{H}_5\text{C}=\text{NH})_2\text{O}$, when it is dissolved in benzene, a little concentrated sulfuric acid is added, and the whole is kept for 24 hours.¹⁵² Nitriles which resist the usual hydrolyzing agents are converted almost without exception to the corresponding amides on prolonged heating with alcoholic caustic. Nitriles in general are converted to amides when treated with 3% alkaline hydrogen peroxide, although in some instances in very small yield. Phenylcrotononitrile is converted almost quantitatively to α,β -phenylglycidamide when treated with hydrogen peroxide in aqueous acetone solution in the presence of sodium carbonate:



α,β -Ethylenic nitriles do not all form glycidamides with hydrogen peroxide.

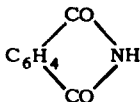
Aromatic amides may be obtained in excellent yield through the reaction of urea chlorides with aromatic hydrocarbons in carbon disulfide solution in the presence of aluminum chloride:¹⁵³



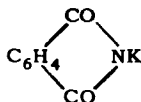
The presence of alkyl substituents in the nucleus facilitates the reaction. The quantity of aluminum chloride used should not be excessive in order to avoid the migration of such substituents. It is not necessary to employ the finished chloride, and it is often of advantage to generate the chloride *in situ* by passing vapors of cyanic acid and hydrogen chloride simultaneously through the liquid.¹⁵⁴ Cyanic acid vapors are generated by heating cyanuric acid in a combustion tube. A current of hydrogen chloride is passed through the tube to carry the cyanic acid vapors into the reaction vessel. The carbamic group enters the para posi-

tion, although a small proportion of the *ortho* isomer is also formed. Alkyl urea chlorides react in a manner similar to carbamic chloride.

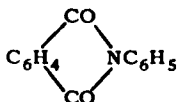
Phthaiimide,



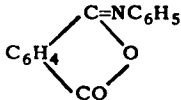
may be prepared by the action of gaseous or aqueous ammonia on phthalyl chloride or phthalic anhydride at 300°. ¹⁵⁵ The compound gives potassium phthalimide,



when treated with alcoholic potassium hydroxide.
sym-Phthalanil,



is obtained through the reaction of aniline with phthalic acid. *asym*-Phthalanil,



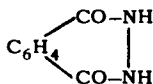
is obtained by the action of acetyl chloride on phthalanilic acid. ¹⁵⁶

Aromatic *acyl hydrazines* may be prepared by methods similar to those which serve for the preparation of amides. They may be obtained, for example, by heating an ester of the acid with hydrazine, ¹⁵⁷ and from hydrazine and an acyl halide in the presence of caustic. ¹⁵⁸

sym-Dibenzoylhydrazine, $C_6H_5CONHNHCOC_6H_5$, results when an excess of hydrazine is made to react with ethyl benzoate. The compound is formed also through the reaction of benzoyl chloride with hydrazine in the presence of sodium hydroxide. It gives a potassium salt, $C_6H_5CONKNHCOC_6H_5$, when boiled with alcoholic potassium hydroxide. The corresponding silver salt, treated with iodine, gives azodibenzoyl, $C_6H_5CON=NCOC_6H_5$. ¹⁵⁹

Tri- and tetrabenzoylhydrazines are obtained by continued benzoylation of dibenzoylhydrazine. ¹⁶⁰

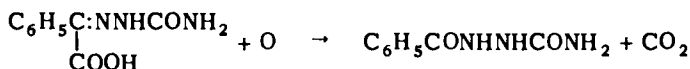
Phthalylhydrazine,



is obtained from phthalic anhydride and hydrazine hydrate.

Acyl azides are formed by the action of nitrous acid and acetic acid on acyl hydrazines. They are formed also by the action of potassium azide on acyl chlorides in moist acetone. ¹⁶¹

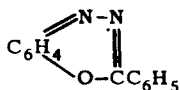
Acyl semicarbazides are formed when semicarbazones of aromatic α -keto acids are oxidized with a solution of iodine in potassium iodide containing sodium carbonate:



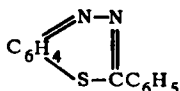
The oxygen in amides may be replaced with chlorine by use of phosphorus pentachloride or carbonyl chloride. Dimethylbenzamide chloride, $\text{C}_6\text{H}_5\text{CCl}_2\text{N}(\text{CH}_3)_2$, has been obtained in this manner from dimethylbenzamide. Benzanilide gives benzanilide imidochloride, $\text{C}_6\text{H}_5\text{CCl}=\text{NC}_6\text{H}_5$, by the action of phosphorus pentachloride.¹⁶²

Benzamido chloride, $\text{C}_6\text{H}_5\text{CCl}_2\text{NH}_2$, is formed when hydrogen chloride is conducted into an ethereal solution of benzonitrile.¹⁶³

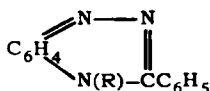
Dibenzohydrazide hydrochloride, $\text{C}_6\text{H}_5\text{CCl}=\text{NN}=\text{CClC}_6\text{H}_5$, is obtained by the action of phosphorus pentachloride on *sym*-dibenzoylhydrazine. The compound can be readily converted to heterocyclic bodies. Thus, diphenyloxadiazole,



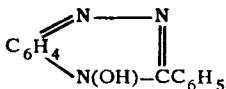
is obtained when the compound is heated with water, and diphenylthiodiazole,



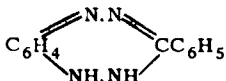
is formed when it is made to react with phosphorus pentasulfide. Reaction with ammonia, or primary amines results in the formation of phenyltriazoles,



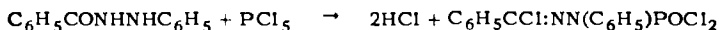
Hydroxylamine gives N-hydroxydiphenyltriazole,



and hydrazine gives diphenyldihydrotetrazine,¹⁶⁴

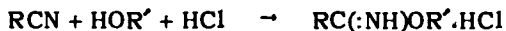


while hydrazineimidochloride is formed when the reaction product of benzoylphenylhydrazine and phosphorus pentachloride is treated with alcohol¹⁶⁵



Imino Ethers

Nitriles in general react with alcohols in the presence of hydrogen chloride to form salts of imino ethers:¹⁶⁶



Imino ethers may be obtained also through the reaction of nitriles with phenols in the presence of hydrogen chloride.

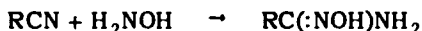
In preparing imino ether hydrochlorides it is necessary to use a slight excess of both the alcohol and hydrogen chloride. The mixture of nitrile and alcohol is cooled, and hydrogen chloride is passed through the liquid until the proper quantity has been absorbed. The liquid is allowed to stand a few days and is then placed in a desiccator over concentrated sulfuric acid and solid caustic.

The free imino ether may be obtained by adding the powdered imino ether hydrochloride to an excess of well-cooled 33% potassium carbonate with good agitation. The compound may be isolated by extraction with ether. The free imino ethers are not stable and gradually decompose. Salts of imino ethers are hydrolyzed in aqueous ammonia, or in the presence of acids, to an ester and ammonia.¹⁶⁷

Hydriodides of imino ethers may be obtained by heating acid amides with alkyl iodides and cuprous oxide, lead oxide, or potassium carbonate.¹⁶⁸

Amidoximes

Amidoximes are formed when hydroxylamine reacts with nitriles:



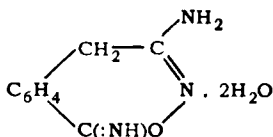
The reaction generally proceeds slowly, but in exceptional cases, as with chlorinated acetonitriles, rapid reaction has been observed. Many aromatic amidoximes have been made by this method.¹⁶⁹

Benzamidoxime results when benzonitrile is heated at 60 to 80° with an aqueous alcoholic solution of hydroxylamine;¹⁷⁰ *p*-toluic amidoxime results similarly when the corresponding nitrile is heated with an alcoholic solution of hydroxylamine at 80-90° for 6 hours. Phenylacetamidoxime, $\text{C}_6\text{H}_5\text{CH}_2\text{C}(\text{:NOH})\text{NH}_2$, has been obtained by heating benzyl cyanide with an aqueous alcoholic solution of hydroxylamine at 40-50° for 36 to 48 hours.¹⁷¹ Cinnamic amidoxime, $\text{C}_6\text{H}_5\text{CH}=\text{CHC}(\text{:NOH})\text{NH}_2$, has been obtained by heating the nitrile with an aqueous alcoholic hydroxylamine at 60 to 70° for a few days.¹⁷²

Phenylnitroacetamidoxime, $\text{C}_6\text{H}_5\text{CH}(\text{NO}_2)\text{C}(\text{:NOH})\text{NH}_2$, has been prepared from the sodium compound of phenylnitroacetonitrile and hydroxylamine hydrochloride in aqueous solution.¹⁷³

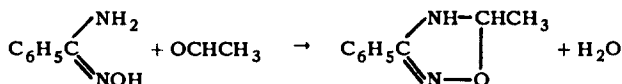
Cinnamaldehyde cyanohydrin is decomposed to cinnamaldehyde when heated with hydroxylamine, and the final product of the reaction is cinnamaloxime. Phenylvinylhydroxethenylamidoxime, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}(\text{OH})\text{C}(\text{:NOH})\text{NH}_2$ is obtained, however, when the reaction is carried out at 70°.¹⁷⁴

o-Cyanobenzyl cyanide reacting with hydroxylamine gives orthophthaleneaminoimidoxime,¹⁷⁵

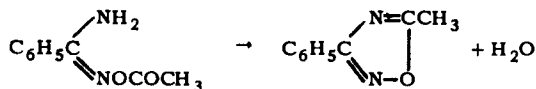


Amidoximes are formed also by the action of hydroxylamine on thioamides, imino ethers, and amidines.

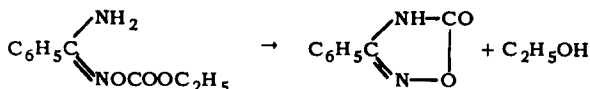
Amidoximes condense with aliphatic aldehydes forming hydrazoximes:



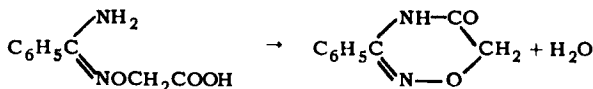
Acyated derivatives of amidoximes of the type $\text{C}_6\text{H}_5\text{C}(\text{NH}_2)=\text{NOCOCH}_3$ and esters of the type $\text{C}_6\text{H}_5\text{C}(\text{NH}_2)=\text{NOCH}_2\text{COOH}$ are known. Acylated derivatives, heated above their melting point, lose the elements of water and form azoximes:



The ethoxy carbonate yields benzenyloxyazoxime:

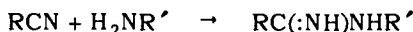


The hydroxyacetic ester gives a keto oxadiazine:



Amidines

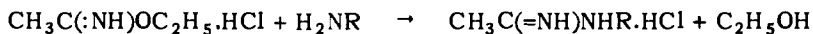
The reaction of ammonia or an amine with a nitrile in the presence of the hydrochloride of the amine leads to the formation of an amidine:¹⁷⁶



Amidines are formed also when nitriles are added to a solution of potassium amide in liquid ammonia.¹⁷⁷

Aromatic nitriles react with sodium amide to form the sodium derivative of the corresponding amidines. Yields are low when the nitrile is heated with sodium amide, but better yields are obtained when a liquid diluent such as toluene is employed.¹⁷⁸ Amidines are also formed through the reaction of nitriles with amines in the presence of metallic sodium.¹⁷⁹

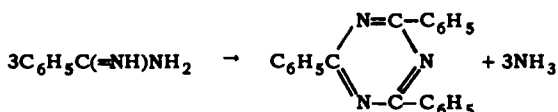
Amidines form readily through the interaction of ammonia or amines with imino ether hydrochlorides:



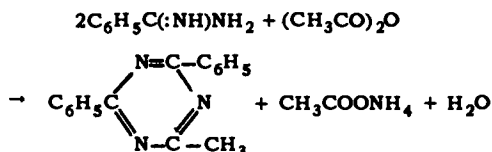
Amidines of aromatic carboxylic acids also result from the reaction of amines with aromatic imidochlorides and thioamides.

Amidines are converted quantitatively to thioamides by treatment with hydrogen sulfide, or by heating at 100° with carbon disulfide.

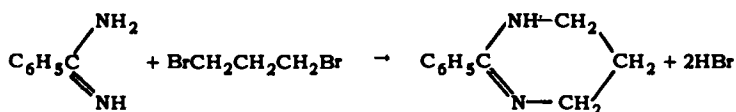
When benzamidine is heated alone, it is converted to cyaphenine:



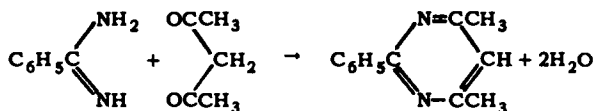
when heated with acetic anhydride it gives diphenylmethyltriazine:¹⁸⁰



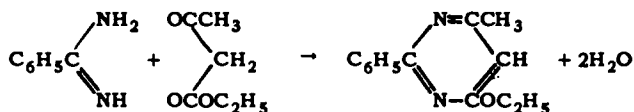
Trimethylenebenzamidine is obtained by reaction with trimethylene bromide:¹⁸¹



Acetylacetone reacting with benzamidine gives phenyldimethylpyrimidine:

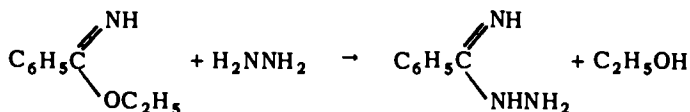


with acetoacetic ester, phenylmethylethoxypyrimidine is obtained:

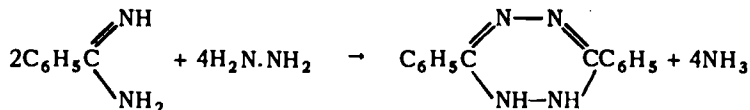
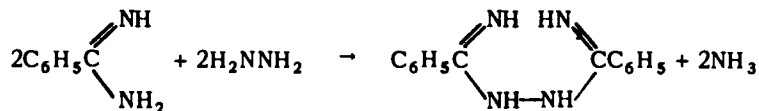


Hydrazidines

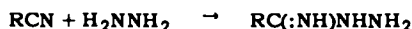
Hydrazidines of aromatic carboxylic acids result when hydrazine reacts with imonoethers:



Dibenzylhydrazidine and diphenyldihydrotetrazine are formed in the reaction of benzamidine with hydrazine:



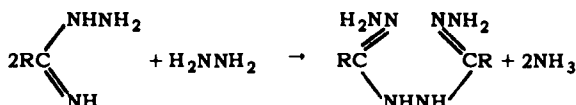
Nitriles react with hydrazine hydrate, apparently first forming a hydrazidine:



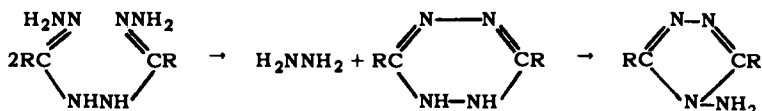
At the temperature at which the reaction rate is appreciable, two molecules of the hydrazidine combine to form a dibenzylhydrazidine:¹⁸²



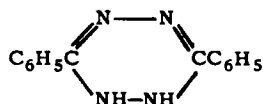
An N-aminodibenzylhydrazidine forms through the reaction of two molecules of the hydrazidine with one of hydrazine:



The compound may undergo ring closure, forming an N-aminotriazole:

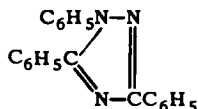


Benzonitrile heated for several days with anhydrous hydrazine forms exclusively diphenyldihydrotetrazine,



while with a cold alcoholic solution of hydrazine hydrate it gives diphenyldihydrotetrazine and diphenyl tetrazine. *o*-Tolunitrile does not react with anhydrous hydrazine, but the para isomer reacts on several days heating. The meta isomer reacts readily to form dimetatolyldihydrotetrazine. β -Naphthonitrile also gives a dihydrotetrazine with hydrazine.¹⁸³

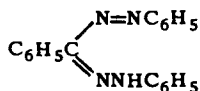
Benzonitrile reacts with phenylhydrazine in benzene solution in the presence of a little of the sodium compound of phenylhydrazine to form C-diphenyl-N-phenyl-1,2,4-triazole:



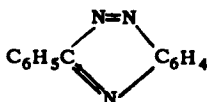
Triazoles are formed similarly with *o*- and *p*-tolunitriles and with α - and β -naphthonitriles.¹⁸⁴

Substituted phenylhydrazines, $\text{C}_6\text{H}_5\text{NRNH}_2$, reacting with nitriles, give N-substituted hydrazidines.¹⁸⁴

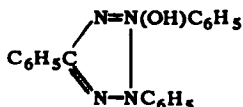
Formazylbenzene,



is obtained through the reaction of phenylhydrazine and benzamidoxime.¹⁸⁵ A mixture of sulfuric and glacial acetic acids converts the compound to phenyl 1,2,4-benzotriazine,



while oxidation leads to the formation of triphenyltetrazolium hydroxide,



Hydroxamic Acids

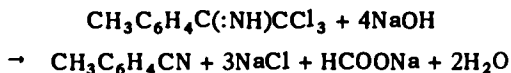
Hydroxamic acids, $RC(:NOH)OH$, are obtained through the reaction of the corresponding acyl chloride or ester with hydroxylamine. Thus, benzhydroxamic acid, $C_6H_5C(:NOH)OH$, is formed by the reaction of hydroxylamine and benzoyl chloride, and phenylacethydroxamic acid, $C_6H_5CH_2C(:NOH)OH$, results from the reaction of ethyl phenylacetate and alcoholic hydroxylamine.¹⁸⁶

Alkyl ethers of hydroxamic acids, $RC(:NOH)OAlk$, are obtained from the corresponding imino ethers by reaction with hydroxylamine hydrochloride, or from the acylated alkyl ethers of hydroxamic acids by hydrolysis.¹⁸⁷ These compounds occur in two stereoisomeric modifications.

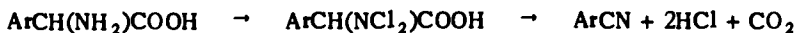
The chlorides of hydroxamic acids have been obtained through the reaction of chlorine with the corresponding aldoximes in chloroform solution.¹⁸⁸

AROMATIC NITRILES

Aromatic nitriles may be prepared by many of the methods utilized for the preparation of aliphatic nitriles. There are also methods, however, which are suitable primarily for the preparation of aromatic nitriles. The latter are formed when trichlorides of the type $ArCCl_3$ are distilled with acid amides;¹⁸⁹ they result also through the fission of trichloroacetamino compounds obtained from aromatic hydrocarbons by reaction with trichloroacetonitrile in the presence of aluminum chloride.¹⁹⁰



α -Aminophenylacetic acids heated with sodio-*p*-toluenesulfochloroamides yield aromatic nitriles, a dichloroamino acid apparently being formed first:¹⁹¹



Nitriles are formed when a formanilide is heated with concentrated hydrochloric acid and zinc dust,¹⁹² or when vapors of a formanilide or an aromatic amine formate are passed over active carbon heated to 425°.¹⁹³

Halogens attached to an aromatic nucleus are not, as a rule, readily replaced with the cyano group. Replacement may be effected by heating the aromatic halo compound with cuprous cyanide, or a mixture of an alkali cyanide and a copper salt, at an elevated temperature in an autoclave.¹⁹⁴ Replacement may also be effected by passing the halo compound over strongly heated potassium ferrocyanide. When halo nitrobenzenes are heated with alcoholic potassium cyanide to 200-300°, a nitro group is removed from the nucleus, and replaced with a cyano group. The cyano group does not enter the position originally occupied by the nitro group, but an adjacent position.¹⁹⁵ At the temperature of the reaction the nitrile is hydrolyzed to the corresponding acid.

The sulfonic group is replaced with a cyano group when a mixture of an aromatic sulfonic acid with potassium cyanide or ferrocyanide is distilled. Nitriles may also be obtained by distilling mixtures of triaryl phosphates with potassium cyanide or ferrocyanide.

The diazo group in aromatic diazonium compounds may be replaced with the cyano group by reaction with cuprous potassium cyanide:¹⁹⁶



A molecular equivalent of cuprous salt is required in this reaction.

The procedure is to heat a mixture of the aqueous potassium cyanide and copper sulfate to 90° and to run in the solution of diazonium chloride slowly. Upon the completion of the reaction the mixture is distilled, and the oily layer is washed successively with dilute caustic soda and sulfuric acid, and the nitrile is isolated by fractional distillation.

The sparingly soluble diazonaphthalenesulfonic acids are added in portions to the hot cuprocyanide solution. The nitrile formed may be isolated by salting out, or by evaporating the solution to dryness and extracting the nitrile with alcohol.¹⁹⁷ Nitriles of the anthraquinone series may also be prepared by this method.¹⁹⁸ Diamines, such as 4,8-dichloro-1,5-diaminoanthraquinone, can be tetrazotized and converted to dicyanides.¹⁹⁹

Replacement of the diazo group with the cyano group can also be effected by the reaction of the diazo compound with an alkali cyanide in the presence of freshly precipitated copper powder in catalytic amounts. The precipitated copper may be prepared through the reaction of zinc dust with copper sulfate in aqueous solution.²⁰⁰ The reaction proceeds at a lower temperature than that with cuprous potassium cyanide, but the yields are sometimes lower than those obtained by use of cuprous double cyanide.

Nuclear synthesis of nitriles may be effected through the reaction of cyanogen halides, or cyanogen with aromatic hydrocarbons in the presence of aluminum chloride.²⁰¹ Reaction with benzene leads to the formation of benzonitrile:



Early efforts gave disappointing results, in part because the cyanogen halide largely trimerized during the reaction. An improved procedure,²⁰² utilizing freshly prepared cyanogen bromide, gave nearly quantitative yields of nitrile with many hydrocarbons. The bromide was added to a suspension of anhydrous

aluminum chloride in the hydrocarbon, and the mixture was heated to boiling under reflux until hydrobromic acid ceased to be evolved. The reaction mixture was then cooled, crushed ice was added, and the hydrocarbon mixture was separated and fractionally distilled to isolate the nitrile.

Aromatic nitriles may be obtained through the reaction of aromatic hydrocarbons with mercuric fulminate, $(\text{C}=\text{NO})_2\text{Hg}$, in the presence of anhydrous aluminum chloride. Benzaldoxime has been obtained in this reaction from benzene and mercuric fulminate by substituting hydrated aluminum chloride for the anhydrous compound.²⁰³

Cyanohydrins of aromatic aldehydes, $\text{ArCH}(\text{OH})\text{CN}$, may be prepared by direct reaction with hydrocyanic acid. Benzaldehyde cyanohydrin has been made through the reaction of the aldehyde with nascent hydrocyanic acid produced by adding sulfuric acid to the solution of alkali cyanide in water.²⁰⁴ Cyanohydrins of *p*-nitrobenzaldehyde, anisaldehyde, and other aromatic aldehydes, as well as of benzyl, have also been prepared by the same method.²⁰⁵ Salicylaldehyde cyanohydrin has been prepared by the direct reaction of the aldehyde and hydrocyanic acid.²⁰⁶ Cyanohydrins of *p*-hydroxy- and *o*-chlorobenzaldehydes and other aromatic aldehydes have also been prepared by this method.²⁰⁶

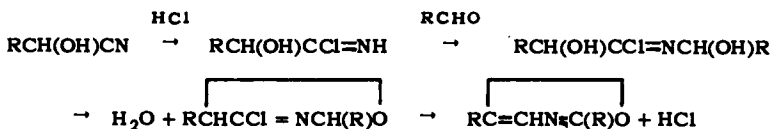
Aromatic aldehyde cyanohydrins may be obtained through the reaction of the bisulfite compound of the aldehyde with alkali metal cyanides.²⁰⁷ This method is generally preferable because the reaction proceeds readily and the yields are satisfactory.

In the preparation of benzaldehyde cyanohydrin from potassium cyanide and the bisulfite compound of benzaldehyde, bis-(α -cyanobenzoyloxy)-phenylmethane,

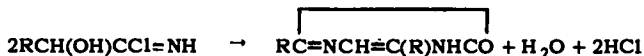


is formed as a by-product. This compound also forms when benzaldehyde and benzaldehyde cyanohydrin react in alcoholic solution in the presence of hydrogen chloride.²⁰⁸

Oxazoles result from the interaction of benzaldehyde or substituted benzaldehydes with their cyanohydrins in the presence of hydrogen chloride:²⁰⁹



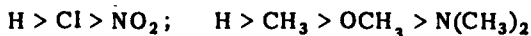
Oxazoles form most readily in the absence of moisture. 3-Keto-2,5-diaryl-3,4-dihydro-1,4-diazepine form through the condensation of two molecules of cyanohydrin in the presence of hydrogen chloride:²¹⁰



The cyanohydrins of aryl aliphatic aldehydes, such as phenylacetaldehyde, are obtained by the usual method of formation of aliphatic cyanohydrins, namely by the reaction of the aldehyde with hydrocyanic acid in the presence of a small amount of basic substance which acts as a catalyst.²¹¹

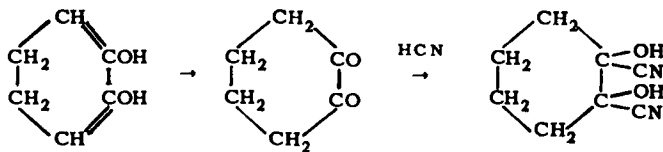
The reactivity of substituted aromatic aldehydes toward hydrocyanic acid is

lower than that of benzaldehyde.²³⁷ The deactivating influence of certain substituents in increasing order is as follows:

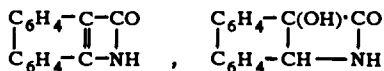


Aryl aliphatic ketones react with difficulty with hydrocyanic acid. Acetophenone cyanohydrin has been obtained in low yield by agitating a mixture of a concentrated ethereal solution of acetophenone with an aqueous solution of potassium cyanide and passing through it a current of gaseous hydrogen chloride.²¹²

Benzoquinone reacts with nascent hydrocyanic acid forming 2,3-dicyanohydroquinone. A molecule of quinone is reduced to hydroquinone in the process.²¹³ Dihydroresorcinol combines with two equivalents of hydrocyanic acid to form dihydroresorcinol dicyanohydrin:²¹⁴

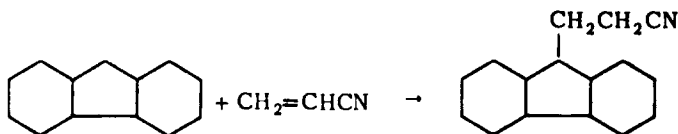


Phenanthraquinone reacts with 30% aqueous hydrocyanic acid to form phenanthraquinone dicyanohydrin.²¹⁵ The compound is hydrolyzed to phenanthranil and hydroxydihydrophenanthranil,



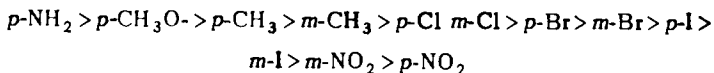
The reaction of phenanthraquinone with more concentrated hydrocyanic acid does not proceed until the mixture of the compounds is heated to 100°, when an stereoisomeric dicyanohydrin is formed.

Certain β -arylethylene cyanides are obtained by the cyanoethylation reaction with acrylonitrile.²¹⁶ An example is offered by fluoreneethyl cyanide, which is obtained from fluorene:



The reaction is carried out in the presence of a basic substance, such as trimethylbenzylammonium hydroxide (Triton B). Addition compounds of this type have been obtained also with indene, anthracene, 2-nitrofluorene, and ω,ω -dimethylbenzofulvene.

The hydrolysis and related reactions of the cyano group in nitriles proceeds with varying ease, depending on the character of the nitrile. The activating effect of various substituents in decreasing order is as follows:



It is evident that electron release from the nucleus facilitates the reaction by bringing about the intramolecular ionization of the intrinsically very stable cyano group.

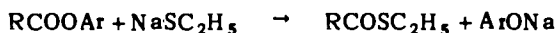
AROMATIC THIO AND DITHIO CARBOXYLIC ACIDS

Aromatic thiol acids are formed in the form of their potassium salt, through the reaction of aromatic acid chlorides with alcoholic potassium sulfide:²¹⁷



Thiosalicylic acid is obtained in the form of its acetylated derivative by the reaction of acetyl salicyloyl chloride with sodium acid sulfide. Aromatic acid anhydrides and esters also give thio acids by reaction with potassium sulfide. Thio acids may be obtained also through the reaction of aryl magnesium halides with carbon oxysulfide. In this reaction triphenylcarbinol is formed as a by-product.

Thiocarboxylic acids are obtained, further, by heating carboxylic acids with phosphorus pentasulfide.²¹⁸ Thiolcarboxylic esters result when aryl esters of carboxylic acids are heated with alkali mercaptides:²¹⁹



Benzoyl sulfide, $\text{C}_6\text{H}_5\text{COSCOC}_6\text{H}_5$, is obtained by the reaction of two molecular proportions of benzoyl chloride with one of sodium sulfide. The compound is obtained also by exposing an ethereal solution of thiobenzoic acid to air,²²⁰ or on oxidizing salts of thiobenzoic acid with potassium ferricyanide.²²¹

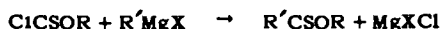
Benzoyl tri- and tetrasulfides are obtained by the action of sulfur chloride, S_2Cl_2 , or iodine on potassium thiobenzoate; these compounds are also formed by the action of hydrogen peroxide and thiobenzoic acid.²²²

Aryl thiosulfites, $(\text{RCOO})_2\text{S}_2$, are obtained by the action of sulfur chloride on metallic salts of aromatic acids.²²³

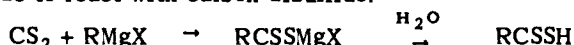
Thioamides are formed when hydrogen sulfide is passed through an alcoholic solution of nitriles containing ammonia.²²⁴ Aromatic thioamides are also formed when benzylamines are heated with sulfur at 180° .²²⁵

Aromatic thioimino ethers are obtained in the form of their hydrochlorides through the reaction of mercaptans with aromatic nitriles in the presence of hydrochloric acid.

Carbothionic esters are formed when chlorothiocarbonic esters are made to react with Grignard reagents:²²⁶



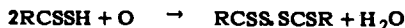
Aromatic dithio acids, ArCSSH , are obtained in the form of their potassium salts when aryl trichloromethanes are heated with alcoholic potassium sulfide.²²⁷ Compounds of this type are obtained also when aromatic Grignard compounds are made to react with carbon disulfide:²²⁸



Dithio acids further result from the reaction of hydrogen persulfide with aromatic aldehydes in the presence of zinc chloride.¹⁰⁸

Dithiosalicylic acid, $\text{HOC}_6\text{H}_4\text{CSSH}$, is formed when hydrogen chloride is passed through a solution of salicylaldehyde in benzene containing hydrogen sulfide.

Dithiocarboxylic acids are readily oxidized to thioacyl derivatives; oxidation may be effected simply by exposing the compounds to air:



Dithiobenzoic acid reacts with hydroxylamine to form thiobenzhydroxamic acid, $\text{C}_6\text{H}_5\text{C}(\text{NOH})\text{SH}$. The compound is unstable.

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CHAPTER 26

AROMATIC AMINES AND RELATED COMPOUNDS

AROMATIC AMINES

Methods of Preparation

The direct introduction of the amino group into an aromatic compound may be effected in a few exceptional cases by heating the compound with hydroxylamine hydrochloride in the presence of anhydrous aluminum chloride or anhydrous ferric chloride.¹ The yield of amine is very low in this reaction. Substitution has been effected by passing a mixture of the vapors of the aromatic compound and ammonia over a heated catalyst.² This method also gives very unsatisfactory yields. An amino group may be introduced into certain derivatives of naphthalene and anthraquinone by melting with sodium amide. The success of the reaction is dependent upon the presence of at least one amino or hydroxyl group in the nucleus. The amino group enters the 5-position in naphthalene with respect to the hydroxyl group or amino group initially present.³

An amino group may be introduced into an aromatic compound by *nitration* followed by *reduction*, and this is the most important method for the preparation of aromatic amines.

Amines by Reduction of Nitro Compounds

Reduction of the nitro compounds to amines may be effected by various methods. Reduction may be brought about, for example, by use of sulfides of alkali metals or ammonia; by the combined action of certain metals and hydrochloric acid, and by electrolysis, or catalytically.

*Reduction by Use of Sulfides*⁴

Reduction of a nitro group to an amino group can be effected by the action of an alcoholic solution of ammonium sulfide. The reaction is generally carried out by dissolving the nitro compound in aqueous alcoholic ammonia and conducting a stream of gaseous hydrogen sulfide through the solution. In many cases reduction proceeds smoothly at room temperature; a hydroxylamine derivative is obtained in such cases if the reduction is carried out under strong cooling. It is often necessary, however, to carry out the reaction in closed vessels at an elevated temperature under pressure.⁵ The method is especially suitable for the partial reduction of di- and polynitro compounds. The reagent is introduced gradually, and the reaction is carried out at the lowest possible temperature.

Usually a single nitro group in these compounds is converted to an amino group by the treatment.⁶ Exceptionally, diamino compounds result from trinitrobenzene and 3,5-dinitrobenzoic acid.⁷

Mononitro compounds are reduced slowly by this method,⁸ while di- and polynitro compounds react readily as a rule. Nitro groups in *ortho* position with respect to substituents are reduced less readily, although there are exceptions to this rule. Picric acid gives picramic acid,⁹ and 2,4-dinitroaniline gives a mixture of 4-nitro-*o*-phenylenediamine and 2-nitro-*p*-phenylenediamine.¹⁰ *o,p*-Dinitrobenzoic acid also yields both the isomeric nitroaminobenzoic acids.¹¹

If the compound contains labile nitro or halo groups, these may be replaced by the SH group during the reaction.¹² 2,3-Dinitrotoluene is converted to dinitroditolyl sulfide when treated with alcoholic ammonium sulfide.¹³ Halonitro and dinitro compounds are reduced only if the substituents do not occupy adjacent positions in the nucleus.

Some nitro compounds must be reduced in ammoniacal solution with the exactly calculated quantity of hydrogen sulfide. Thus, dinitrophenol can be reduced successfully to nitroaminophenol only by treating the very finely divided sodium salt in ammoniacal suspension with the exactly calculated quantity of hydrogen sulfide at 60°.

Nitroso phenols and some derivatives of *p*-nitrosoaniline are also readily reduced to the corresponding amino compounds by treatment with alcoholic ammonium sulfide.¹⁴

Reduction of aromatic nitro compounds to the corresponding amino compounds can also be carried out with *sodium sulfide* or *sodium hydrosulfide*. These agents have a greater reducing power than ammonium sulfide, and have the advantage that no free sulfur separates out during the reaction.¹⁵

Sodium hydrogen sulfide in aqueous alcoholic solution converts dinitroazo- and dinitroazoxybenzene into aminoazobenzene, whereas ammonium hydrogen sulfide converts these compounds to dinitrohydrazobenzene.¹⁶

Acid sulfides convert 5-nitrotetralin to 5-aminotetralin, but have no effect on 6-nitrotetralin.

Sodium disulfide, Na₂S₂, may also be used for the reduction of nitro compounds to amino compounds. The reaction proceeds as follows:

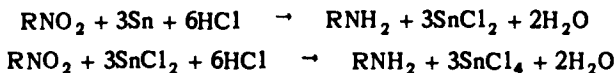


The disulfide is prepared by heating under reflux a solution of one molecular equivalent of sodium sulfide in five times its weight of water with an atom equivalent of sulfur.

Sodium hydrosulfite, Na₂S₂O₄, has also been used for the reduction of nitro groups to amino groups. This compound readily effects the reduction of *o*- and *p*-nitrophenols.¹⁷ *Ortho* and *meta* nitrobenzaldehydes may also be converted to the corresponding amino benzaldehydes by treating their aqueous suspensions with sodium hydrosulfite. Other nitro compounds which cannot be otherwise reduced to amines, or can only be reduced with difficulty, are readily converted to amines by treatment with sodium hydrosulfite. Examples of such compounds are 4-nitro-1-acetylcoumarin and nitropyrazole derivatives. 2-Nitrophenanthraquinone and 3,4-nitrophenyl-1-arsinous acids are also reduced to amino derivatives with sodium hydrosulfite.¹⁸

Reduction with Tin, Zinc, and Copper

The reduction of nitro compounds to primary amines may be effected successfully by the use of *tin* and hydrochloric acid.¹⁹ The reduction proceeds as follows:



The nitro compound is mixed with the finely divided metal, and concentrated hydrochloric acid is added gradually. The temperature of the mixture is so controlled as to avoid too vigorous a reaction, which may result in the elimination of the nitro groups as ammonia. In some instances the amine combines with the tin chloride to form a double compound. The amine may be separated by steam distillation if it is volatile with steam; otherwise the reaction mixture is diluted with water, partially neutralized, and the tin is precipitated as the sulfide. The solution is filtered off, concentrated by evaporation, and excess caustic added to liberate the amine. One and a half times the theoretically required amount of metallic tin should be employed for complete reduction. This method makes possible the reduction of all nitro groups in di- and polynitro compounds.

The use of some acetic acid presents an advantage in dealing with nitro compounds of low solubility in concentrated hydrochloric acid. 4-Nitro-*o*-toluidine may be made, by use of this modification, from 2,4-dinitrotoluene;²⁰ and 2-nitro-*m*-toluidine may be obtained from 2,3-dinitrotoluene. A mixture of the isomeric nitroamines is formed from 2,4-dinitro- and 2,5-dinitrotoluene.²¹

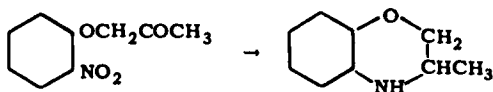
Selective reduction of polynitro compounds may be accomplished by use of the theoretically required amount of stannous chloride for partial reduction, and aqueous or alcoholic hydrochloric acid.²² A solution of stannous chloride in glacial acetic acid saturated with hydrogen chloride is a vigorous reducing agent. It brings about the reduction of many nitro compounds in the cold, and thus presents an advantage in the reduction of nitro compounds which are resinsified on heating.²³ Reduction with stannous chloride can also be carried out in ethereal solution, since the compound is soluble in ethereal hydrogen chloride.²⁴

It should be noted that whereas ammonium sulfide reduces the *p*-nitro group in *o,p*-dinitro compounds, stannous chloride reduces the *o*-nitro group.²⁵ 2,3-Dinitrotoluene gives 2-nitroaminotoluene when reduced with tin and hydrochloric acid, and 2,5-dinitrotoluene gives both the 2-amino-5-nitro- and 2-nitro-5-amino derivatives.²⁶

The reduction of nitro compounds with tin and hydrochloric acid results in the partial chlorination of the reaction product. The chlorine enters the *o*- and *p*-position with respect to the amino group.²⁷ When *p*-nitrophenetole is reduced by this method without cooling, 3-chloro-*p*-phenetidine is formed as the main product. *p*-Phenetidine may be obtained from *p*-nitrophenetole, however, by reduction with tin and dilute hydrochloric acid.²⁸ Chlorination may take place also during reductions carried out with *stannous chloride* and *acetic anhydride*.²⁹ Nitrobenzene, for example, yields *p*-chloroacetanilide as the principal product; *o*-, *m*- and *p*-nitrophenetole and *o*-nitroanisole also give chlorinated products. *p*-Nitrotoluene, *p*-nitroanisole and *p*-nitrophenetole, on the other hand, give the corresponding amines without the formation of chlorinated compounds. It has been claimed that the formation of chlorinated compounds may be prevented by the addition of graphite, which lowers the hydrogen overvoltage of tin.³⁰

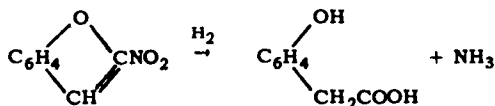
The reverse effect has also been observed, reaction with tin or stannous chloride resulting in the removal of halogens from the nucleus. *m*-Phenylenediamine is obtained, for example, when 4-bromo-1,3-dinitrobenzene is reduced with tin and hydrochloric acid.³¹ Chloronitrosoorcin, reduced with tin and hydrochloric acid, gives aminoorcin; on reduction with stannous chloride alone in absolute alcohol, chloroaminoorcin is formed.³²

Ring formation takes place in the reduction of certain nitro compounds with tin and hydrochloric acid; thus, *o*-nitrophenoxyacetone gives methylphenmorpholin:³³

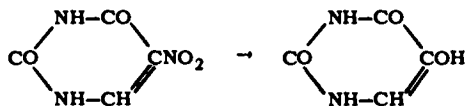


Some nuclearily chlorinated methylphenmorpholin is also formed in the reaction.

In the reduction of the nitro derivatives of heterocyclic compounds, in which the nitro group is attached to a carbon atom with a double bond, the nitro groups are removed in the form of ammonia, with subsequent molecular rearrangements.³⁴ *o*-Hydroxyphenylacetic acid results, for example, from the reduction of 1-nitrocoumarin:³⁵



In other cases the nitro group becomes replaced with hydroxyl, as in the reduction of nitrouracil:³⁶



Occasionally also the nitro group is converted to a hydroxylamino group, hydrolysis of the resulting compound giving a ketone:



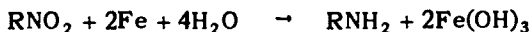
The reduction of aromatic nitro compounds can be effected by the use of zinc and hydrochloric acid, acting on the nitro compound in alcoholic solution. Since, however, nuclearily chlorinated compounds are formed in this reaction, the method cannot be recommended. Reduction may be brought about with zinc dust and alkali in alcoholic solution.³⁷ This method is suitable for the reduction of nitro compounds soluble in aqueous alkalies, and nitro compounds that are unstable in acid solution.³⁸

Nitrated ketones and acylnitroamines can be reduced to the corresponding amines by boiling with a suspension of zinc dust and ammonium chloride in 90% alcohol.³⁹

The reduction of nitro compounds to amino compounds may be accomplished also by use of metallic copper and acid.

Reduction with Iron; Béchamp-Brimmeyer Reduction

Nitro compounds may be reduced very effectively with iron turnings and an acid.⁴⁰ Hydrochloric acid is generally used for the purpose, and it is found that the quantity of acid employed may be reduced to 1/40 of that required for the conversion of the iron utilized in the reaction to chloride. It appears probable that ferrous chloride is first formed and acts as a carrier in the reduction of the nitro compound by iron and water, the finely divided metal acting as the actual reducing agent.⁴¹



Nearly all nitro compounds, even those resisting the action of other reducing agents, are converted to the corresponding amines by this method. A partial reduction of polynitro compounds is possible by avoiding any excess of acid, and using a small amount of water. No nuclearly chlorinated compounds are formed on reduction of nitro compounds by this method.

In carrying out the reduction with iron in the industrial scale the following conditions are observed: The reaction vessel is preferably constructed of wrought iron. Cast iron borings or shavings are used in the reaction; they are washed with an organic solvent to remove any grease or oil from the surface of the metal. The iron is ground to a fine powder in a ball-mill. The fines are removed if the iron is to be used in sensitive reactions. The stirrer must extend to the bottom of the reaction vessel and is run with sufficient speed to hold the iron powder in suspension. Reduction is usually carried out at boiling temperatures but with sensitive substances, such as *p*-nitrosodimethylaniline, the reaction temperature is not allowed to exceed 80°.

The method is not suitable for the selective reduction of one of two or more nitro groups present in di- and polynitro compounds.

Reduction with Ferrous Sulfate and Alkali

A mixture of ferrous sulfate and ammonium hydroxide may be employed for the reduction of nitro compounds to amines. The method is well suited for the reduction of acid-sensitive nitro compounds, such as certain nitrated aldehydes, nitrobenzoylformic acid and nitrophenylpropionic acid.⁴² Seven molecular equivalents of ferrous sulfate are generally required for complete reduction. A concentrated solution of the sulfate is heated to boiling and the nitro compound dissolved or suspended in dilute ammonia is added. Boiling is continued with gradual addition of concentrated ammonium hydroxide until the solution remains permanently alkaline. Boiling is continued under partial vacuum, more ammonia being added if the liquid should become acid. The amine formed is isolated by the usual methods. Very sensitive nitro acids may be reduced to amino acids with ferrous sulfate and ammonia in the cold.⁴³ Nitro aldehydes can also be reduced to the highly sensitive amino aldehydes.⁴⁴

m-Aminobenzaldehyde cannot be obtained by this method from the nitro compound. This compound is best prepared in solution through the reduction of the bisulfite compound of *m*-nitrobenzaldehyde with ferrous sulfate and ammonia, or with zinc dust and a mineral acid. It cannot, however, be isolated in the free state, but must be used in solution. The corresponding hydroxy aldehyde is stable.

Reduction with ferrous sulfate may also be accomplished by use of alkali or barium hydroxide.⁴⁵

Miscellaneous Reducing Agents

A mixture of *titanium trichloride* and *hydrochloric acid* reduces nitro compounds readily, and this reagent is employed for the quantitative determination of nitro groups.⁴⁶ *Sodium arsenite*⁴⁷ and sodium hydroxide in conjunction with certain alcohols, such as propyl, isopropyl, butyl and isoamyl alcohols⁴⁸ have also been used for the reduction of nitro groups. Aluminum activated with mercuric chloride is a satisfactory reducing agent of practically neutral reaction.⁴⁹

Hydrazine and *phenylhydrazine* are capable of bringing about the reduction of nitro compounds to amines:



Partial reduction of certain polynitro compounds is possible only with phenylhydrazine; this is true, for example, of *o,o*-dinitrotolan.⁵⁰

Catalytic Reduction

Nitro compounds are smoothly converted to the corresponding amino compounds when their vapors, mixed with hydrogen, are passed over finely divided metals, such as copper, nickel, etc., heated to 200–400°. ⁵¹ Copper would appear to be the most satisfactory catalyst, since it resists catalyst poisons, and does not affect the aromatic nuclei. The optimum temperature for this metal lies between 300 and 400°, and is somewhat higher than that for nickel. Metallic oxides, such as FeO and Fe₃O₄, also possess catalytic power.⁵² Reduction may be effected at ordinary temperature in the liquid phase by use of finely divided platinum or palladium. A satisfactory procedure is to shake an ethereal solution of the nitro compound with the finely divided metal in suspension.⁵³ This method is adapted for the partial reduction of polynitro compounds.

Nitroso compounds can be reduced to amino compounds by hydrogen in the presence of platinum oxide without the intermediate formation of hydroxylamine derivatives.⁵⁴

Nitrobenzene may be reduced to aniline by heating at 150° with carbon monoxide under 150 atmospheres in the presence of iron.

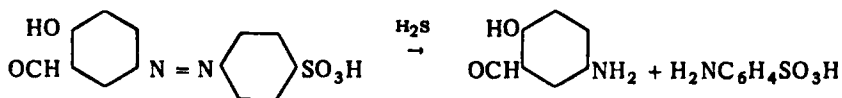
Electrolytic Reduction

Aromatic nitro compounds can be reduced electrolytically.³²⁶ The product of reduction of nitrobenzene in concentrated sulfuric acid is *p*-aminophenol, which is formed through a molecular rearrangement from *β*-phenylhydroxylamine, the original product of the reduction.⁵⁵ When the *para* position in the nitro compound is occupied with a substituent, the product of the reduction is an *o*-aminophenol. The process offers a satisfactory method for the preparation of amino phenols.

Reductive Cleavage of Azo and Hydrazo Compounds to Amines

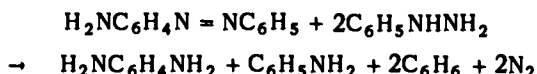
When azo compounds are boiled with a suspension of zinc dust in water, cleavage of the molecule takes place at the nitrogen to nitrogen bond, and

amines are formed.⁵⁶ Reduction may be effected also by use of tin and alcoholic hydrogen chloride,⁵⁷ or with stannous chloride and hydrochloric acid.⁵⁸ When the latter method is used, it is usual to employ two grams of stannous chloride and five cubic centimeters of hydrochloric acid per gram of azo compound to be reduced. The reduction of azo compounds to amines may be accomplished also with alkali polysulfides,⁵⁹ and in some instances even with hydrogen sulfide dissolved in dilute sodium carbonate solution.⁶⁰ 5-Aminosalicylaldehyde may be prepared by this method:



Sodium hydrosulfite also brings about the reduction of azo compounds to amines.⁶¹ Reduction proceeds more readily with this compound than with stannous chloride and hydrochloric acid, and the method is of wide applicability. If the azo compound is insoluble in water, reduction may be carried out in alcohol, in neutral or weakly alkaline solution.

Azo compounds may be converted to amines by other reducing agents, such as fuming hydriodic acid,⁶² titanium trichloride,⁶³ and phenylhydrazine;⁶⁴ this last is converted to benzene in the course of the reaction, with liberation of nitrogen:



Electrolytic reduction of azo compounds has been carried out successfully by using a cathode constructed of tin or an indifferent metal, and adding a small amount of finely divided tin in the cathode compartment.⁶⁵

Reduction of azo compounds may be effected successfully by catalytic methods. Azobenzene, for example, is readily reduced to aniline with hydrogen in the presence of finely divided palladium.⁶⁶ Pyrrole azo compounds have been reduced with platinum black.⁶⁷ Reduction may be brought about also by use of nickel, cobalt, or iron catalysts.

Formation of Amino Compounds by Exchange Reactions

Halogens and nitro and hydroxyl groups joined to an aromatic radical may be replaced with an amino group under certain conditions. The reaction does not proceed readily in general. Halogenated aromatic hydrocarbons, when heated with ammonia, yield only traces of amino compounds, although the reaction takes place more readily in the presence of small quantities of copper salts. Halonitro compounds generally react with ammonia in the absence of catalysts to give amino nitro compounds. Reaction proceeds the more readily, the greater the number of nitro groups attached to the benzene nucleus. Meta nitro compounds fail to react in the absence of a catalyst.⁶⁸ The bromine in bromo-2,4-disulfonic acid may be replaced with an amino group by heating the compound with an alcoholic solution of ammonia at 160–180° in an autoclave.⁶⁹ Halogens

and sulfonic groups may be replaced with an amino group by heating aromatic halo or sulfonic compounds with sodamide.⁷⁰

Phenol may be converted to aniline readily by heating with the double compound of zinc chloride and ammonia, $\text{ZnCl}_2 \cdot \text{NH}_3$, to $300\text{--}350^\circ$.⁷¹ Naphthols undergo this reaction much more readily. p-Nitrosoaniline is formed when p-nitrosophenol is heated on a water bath for half an hour with 15 parts of a 1:2 mixture of ammonium chloride and ammonium acetate.⁷²

The carboxyl group in an aromatic compound may be replaced with an amino group by the Hofmann and the Curtius degradations. The first method converts the acid to the amide, which is heated with bromine and aqueous alkali to obtain the amine. The second method converts the acid to the azide via the hydrazide and this, on boiling, yields a urethane, hydrolysis of which gives the desired amine.⁷³ The direct method, utilizing hydrazoic acid, also gives the desired result.⁷⁴ Another method which may be utilized for the replacement of a carboxyl group with an amino group is to dry distill the calcium salt of the acid to obtain a ketone, which is then converted to its oxime and subjected to the Beckmann transformation to give the acylated amine:

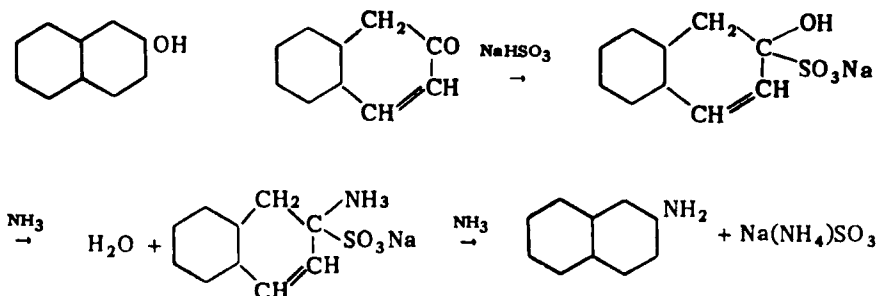


This method is of restricted applicability, since many ketones do not yield an oxime with hydroxylamine.

Oximes of certain ketones derived from cyclohexenes, such as methyl- and dimethylcyclohexenone, trimethylcyclohexenone, or isoacetophorone, give primary anilines by molecular rearrangement when heated with hydrochloric acid.⁷⁵

Bucherer Reaction

Naphthols and many of their derivatives react with ammonia at an elevated temperature in the presence of an alkaline bisulfite to give amines by replacement of the hydroxyl group with an amino group.⁷⁶ The reaction apparently involves the addition of the bisulfite to the keto form of the naphthol, and the subsequent replacement of the hydroxyl group of the addition compound with ammonia:⁷⁷



Reaction may take place at about 90° , or it may proceed satisfactorily only in the neighborhood of 150° , depending on the nature of the naphthol derivative.

The reaction is usually carried out in an autoclave at temperatures ranging from 100 to 150°. In reactions with ammonia, aqueous ammonia containing ammonium bisulfite is employed. This is prepared by saturating concentrated aqua ammonia with sulfur dioxide, then adding an equal volume of concentrated aqueous ammonia to the solution. Yields of the amine are generally quite high. In some instances the reaction results in the formation of an amine sulfonated in the ring.⁷⁸

The Bucherer reaction is applicable to naphthols, many of their derivatives, hydroxyquinolines,⁷⁹ and to resorcinol. Dihydroxy derivatives of naphthalene in which the hydroxyl groups are in different rings usually undergo replacement of one hydroxyl group; the second hydroxyl group may, however, be replaced to a limited extent.⁸⁰

A sulfonic group at position 4 with respect to the hydroxyl group promotes the reaction; one at positions 1, 2 or 3 hinders the reaction. When a sulfo group and a hydroxyl group are in different rings, the former has no effect on the ease with which the reaction proceeds.⁸¹

2,8-Dihydroxynaphthalene-6-sulfonic acid gives 2-amino-8-naphthol-6-sulfonic acid in 80% yield, the hindering effect of the sulfonic group on the 8-hydroxyl group bringing about the replacement of the hydroxyl group in the other ring.

The carbethoxy group has an effect similar to that of the sulfonic group. 2-Hydroxy-3-naphthoic acid undergoes the reaction readily in the temperature range 150–155°, to give principally 2-naphthylamine and some 2,2'-dinaphthylamine.

Preparation of Secondary Amines by the Bucherer Reaction

The replacement of a hydroxyl group by a primary amino group requires more vigorous conditions than replacement with an amino group. The reaction between methylamine and 1-naphthol-4-sulfonic acid, for example, requires heating at 150°, while the reaction of the same compound with ammonia proceeds readily at 90°. ⁸²

The procedure is as follows: The naphthol is dissolved in the minimum amount of boiling water and is mixed at 80–90° with the warm bisulfite solution. If a precipitate separates out, it is brought back into solution by warming on the water bath. The amine, or a mixture of the amine salt with an equivalent of sodium hydroxide, is next added and the mixture is heated under reflux until the reaction is complete; i.e., until no further decrease in the amount of naphthol, or increase in the quantity of the aminated product is observed.

The test for completion of the reaction is carried out in the following manner: A test portion of the reaction mixture is made alkaline to phenolphthalein and the freed amine is removed by steam distillation; the residue is made alkaline to Congo Red and boiled to free it of all sulfur dioxide. The remaining liquid is now titrated with a diazonium salt solution until a drop on a filter paper shows no color in the run-out either with the diazonium salt solution, or with Schaeffer's acid (2-hydroxynaphthalene-6-sulfonic acid). When this point is reached, the precipitated dye is filtered from the test portion and washed with a little saturated sodium chloride solution, the washings being added to the test portion. Sodium acetate is then added, and the solution is again titrated with the same diazonium salt solution. The ratio of the volumes of diazonium salt solution used in the first and second titrations gives the proportion between the aminated compound and the unreacted naphthol.

The introduction of arylamino groups proceeds with greater ease with β -naphthol and its derivatives than with α -naphthol and substituted α -naphthols. Thus, while 2-naphthol-6-sulfonic acid reacts readily with aniline at 100° , 1-naphthol-4-sulfonic acid fails to react at this temperature.⁸³ There is a wide variation in the ease with which aromatic amines replace the hydroxyl group in the Bucherer reaction. Aniline, *o*- and *p*-toluidines, xylydine, aminonaphthol ethers, β -naphthylamine, and benzidine are of a low order of reactivity; *p*-phenetidine, metanilic and sulfanilic acids are of moderate reactivity, while *p*-aminophenol and *p*-phenylenediamine are quite reactive. The arylamination of 1-naphthol has been effected at 100 – 200° by the reaction of the salt of the arylamine with the addition product of 1-naphthol and sodium bisulfite.

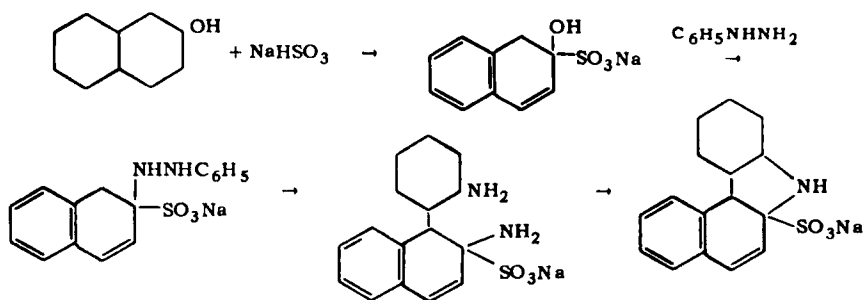
2-Naphthylamines can be used instead of the naphthols in carrying out the arylamination of naphthalene derivatives by the Bucherer method.

While the Bucherer reaction is, in general, reversible, and aniline derivatives of naphthalene can be converted to naphthols, little reversal of the reaction is observed with N-aryl-2-naphthylamines.

Replacement of the Hydroxyl Group with Hydrazines by the Bucherer Reaction

Naphthols are capable of undergoing the Bucherer reaction with hydrazines, giving naphthylhydrazines.⁸⁴ Hydrazines, in effect, react more readily than either ammonia or amines. Hydrazines have been obtained from 1- and 2-naphthol, and from 2,7-dihydroxynaphthalene. More than one hydroxyl group may be readily replaced by hydrazine residues. Dihydrazines are formed, for example, from resorcinol and from 2,3-dihydroxynaphthalene.

The reaction of phenylhydrazine with a naphthol in the presence of sodium bisulfite follows a rather complicated course, giving as the end product a sulfonated dihydro-carbazole.⁸⁵ β -Naphthol, for example, gives a sulfonated dihydro-5,6-benzocarbazole:



This, on heating with an acid or a base, is converted to 5,6-benzocarbazole. 1-Naphthol gives the hydrazine addition product, and this, on treatment with mineral acids, is converted to a carbazole. The reactions with *p*-tolylhydrazine are similar.

N-Alkylated and Arylated Aromatic Amines

N-Alkylated derivatives of aniline and its homologs are formed through the reaction of the amine with alkyl iodides or bromides.

As an example, ethylaniline is prepared by heating under reflux for one to two hours a mixture of 50 grams of aniline and 65 grams ethyl bromide. Water is then added, the unreacted ethyl bromide is distilled off, and an excess of caustic is added to free the amine. The latter is extracted with ether, taken up with aqueous hydrochloric acid and converted to its nitroso derivative. This compound separates out as an oil, and is extracted with ether; the extract is evaporated to dryness and the nitrosoamine is converted to the amine by reduction with tin and hydrochloric acid.

N-Alkylated amines may be obtained also by heating the amine with a mixture of the alcohol and hydrochloric or sulfuric acid in an autoclave at 180–200°. Methyl diphenylamine, $(C_6H_5)_2NCH_3$, is made on the commercial scale by heating diphenylamine with methyl alcohol and hydrogen chloride in an autoclave. Alkylation takes place at a lower temperature, between 125 and 150°, when the bromides or iodides of the amine are heated with alcohols.⁸⁶

N-Alkylated aromatic amines may be obtained by passing vapors of the amine mixed with an alcohol and hydrochloric acid over aluminum oxide heated at 400°.

The primary, secondary and tertiary amines are formed simultaneously in all these reactions.

The alkyl residue in alkylated aromatic amines may be removed rather easily. Thus, dimethylaniline can be completely demethylated by heating at 180° in a current of hydrogen chloride, whereby methyl chloride distills over and aniline hydrochloride remains as a residue.⁸⁷

Separation of Primary, Secondary, and Tertiary Amines from Their Mixtures

Tertiary amines may be separated from a mixture of primary, secondary, and tertiary amines by treatment with acetic anhydride which forms non-basic, alkali-insoluble acetyl derivatives with the primary and secondary amines, but does not react with the tertiary amines.

Secondary amines may be separated from the other amines by treatment in acid solution with sodium nitrite, which gives the water-soluble diazonium salt with the primary amine, and the basic alkali-soluble 8-nitroso compound with the tertiary amine. The secondary amine is converted by this treatment to the non-basic, insoluble N-nitroso compound. This can best be reconverted to the original amine by boiling in hydrochloric acid with thiourea.⁸⁸ Conversion may also be accomplished by reduction with tin and hydrochloric acid, with cuprous or ferrous chloride,⁸⁹ or simply by boiling with hydrochloric acid.

Primary amines may be separated from secondary amines by adding a cold concentrated solution of metaphosphoric acid to a solution of their salts. This causes the precipitation of the primary amines as the metaphosphates, leaving secondary amines in solution.⁹⁰

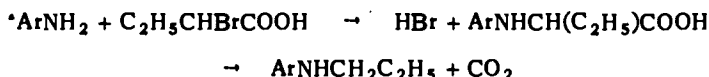
Primary amines may also be separated from secondary and tertiary amines by reaction with ethyl oxalate with which they form oxamino esters. These are less volatile than the free secondary and tertiary bases and may be isolated by distilling off the latter.⁹¹

Secondary alkyl aromatic amines may be prepared in the pure form by alkylating the sodio compounds of acylated primary amines with alkyl iodides.⁹² The acylated amine is dissolved in toluene or xylene, and an equivalent of metallic sodium is added, whereupon the sodio compound separates out as a white precipitate. It reacts readily with alkyl iodides:



Hydrolysis of the resulting acylated amine gives the free secondary amine.

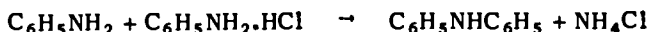
N-Alkylated aromatic amines result on distilling a mixture of an aromatic amine with an α -halo carboxylic acid:⁹³



Alkylidene monoanilines, $\text{ArN} = \text{CHR}$, are readily formed by the condensation of equimolecular amounts of aliphatic aldehydes with amines.⁹⁴ The simpler derivatives polymerize at once, and may undergo further change. Quinoline derivatives have been obtained from some of these polymeric bodies, the compounds having been formed apparently via an intermediate aldol condensation.⁹⁵ The monomeric as well as the polymeric forms of these compounds react additively with hydrocyanic acid giving α -anilido nitriles.

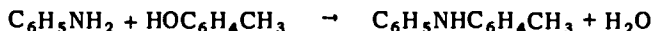
Alkylidene dianilines, $(\text{ArNH})_2\text{CHAlk}$, are obtained through the reaction of an aromatic amine with an aliphatic aldehyde, AlkCHO , in cold aqueous solution. These compounds are hydrolyzed to their components by mineral acids. Methylene dianilines undergo rearrangement to diaminodiphenylmethanes on heating with concentrated hydrochloric acid, or with aniline hydrochloride.⁹⁶

Purely aromatic secondary amines are formed when a mixture of an aromatic amine and an aromatic amine hydrochloride is heated to a sufficiently high temperature. Diphenylamine is obtained, for example, on heating a mixture of aniline and aniline hydrochloride at 200°:



The process is used commercially. Diphenylamine can also be obtained by heating a mixture of phenol and aniline in the presence of zinc chloride. This reaction may be effected by use of calcium chloride or antimony chloride as the condensing agent.

Aromatic secondary amines may be obtained by heating an aromatic amine with a phenol at 250–350° in the presence of calcium chloride:



Triphenylamine, $(\text{C}_6\text{H}_5)_3\text{N}$, is best prepared by heating diphenylamine with phenyl iodide in the presence of a little metallic copper,⁹⁷ or by decarboxylating N-diphenyl-anthranilic acid.⁹⁸

Homologs of Aniline; Hofmann Reaction⁹⁹

Alkylated anilines may be prepared by heating alkyl phenols with ammonia in an autoclave at 250–350° in the presence of calcium chloride or other similar compounds:¹⁰⁰



Secondary amines are also formed in this reaction. Alkyl amines are also formed when a mixture of aniline and an alkyl halide is passed over silica gel at 365–400°.¹⁰¹

The most important method for the preparation of alkylated amines makes use of the *Hofmann transformation*. When the halide of an N-alkyl aniline is heated to 250–350°, the alkyl group migrates into the benzene nucleus, forming a nu-

clearly alkylated amine.⁹⁹ If the nitrogen atom bears more than one alkyl group, all alkyl groups may migrate into the nucleus, one by one:



Quaternary ammonium compounds also undergo the transformation, first giving a nuclearily alkylated tertiary amine, then by steps, a trialkylphenylamine:



Instead of the hydrohalides of the N-alkylated bases, the mixture of an amine with an alkyl halide, or the mixture of salts of primary bases with the appropriate alcohol may be heated to 300°. ¹⁰² A further method is to heat the mixture of an amine and alcohol with zinc chloride.¹⁰³ Phosphorus pentoxide or preferably cobalt chloride or bromide may be substituted for zinc chloride in this reaction.

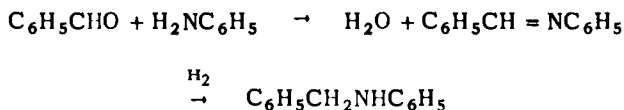
The first alkyl group enters the para position with respect to the amino group, the second and third the two ortho positions. When the para position and both the ortho positions are occupied, the alkyl group enters the meta position. *Para-tert*-butyl and -amyl anilines are formed respectively from isobutyl and isoamyl alcohols and aniline. The yields of alkylated amines decrease with increasing length of the alkyl chain because of increasing olefin formation. Alkylated phenols are formed as a by-product in this reaction. The proportion of phenol formed increases with the number of alkyl groups introduced into the nucleus, until, finally, with penta substitution, the phenol becomes the sole product of the reaction.

Aromatic Amines with Aliphatically Bound Amino Groups

Aromatic amines with an aliphatically bound amino group may be prepared by the methods generally applicable to the preparation of aliphatic amines. They may be obtained readily, for example, through the interaction of the corresponding halide with ammonia or amines;¹⁰⁴ or they may be prepared by hydrolysis of isocyanic esters.¹⁰⁵ Gabriel's method is especially satisfactory for the preparation of this type of amine.¹⁰⁶ Compounds of this type may be obtained, further, through the reduction of nitriles.¹⁰⁷ Benzylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, results for example, together with the secondary and tertiary bi- and tribenzylamines, by the reduction of benzonitrile, $\text{C}_6\text{H}_5\text{CN}$. It is found more satisfactory to convert the nitrile first to the corresponding thioamide by reaction with ammonium sulfide and to reduce the thioamide:¹⁰⁸



Oximes and hydrazones of aromatic aldehydes and ketones may be reduced to primary or secondary amines.¹⁰⁹ The condensation products of aldehyde and ammonia or amines may also be reduced to primary or secondary amines:¹¹⁰



This method is of wide applicability and is highly satisfactory. The formation of tribenzylamine, $(\text{C}_6\text{H}_5\text{CH}_2)_3\text{N}$, on heating benzaldehyde with ammonium formate may be cited as another example of similar reduction reaction.

The Hofmann degradation has been used occasionally for the preparation of alkyl aromatic amines in which the amino group is in the alkyl side chain.¹¹¹ The formation of benzylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, from phenylacetamide,



may be cited as an example of this method.

Halogenated, Nitrated, Nitrosated and Sulfonated Aromatic Amines

The amino group in aromatic amines is readily attacked by many reagents; for this reason it is often necessary to protect the group, by acetylation for example, before subjecting these amines to the action of halogens, oxidizing agents, etc. Substituents may then be introduced without affecting the amino group, and after the completion of the reaction the acetyl group may be removed by heating with caustic. In many cases, the presence of a strong acid is sufficient to prevent attack on the amino group.

Aniline and its derivatives are more readily halogenated than aromatic hydrocarbons.¹¹² When gaseous chlorine is conducted through the aqueous solution of an aniline salt, chlorination proceeds readily and *syn*-trichloroamine results as the final product of the reaction.¹¹³ Similarly, the brominated compound is obtained by adding bromine water to the aqueous solution of an aniline salt. Neither chlorine nor bromine will react, however, at ordinary temperature with aniline in solution in 97% sulfuric acid.¹¹⁴

Partially halogenated derivatives of aromatic amines are best prepared from the corresponding acetylated compounds. Halogenation may be carried out with the compound dissolved in glacial acetic acid or suspended in water. The halogen first enters the para position, and then substitution in the two ortho positions proceeds. Reacting in the presence of concentrated sulfuric acid, chlorine and bromine give meta halogenated anilines.¹¹⁵ While it is possible to introduce at most three halogen atoms in aniline itself, halogenation of meta halo anilines leads to the formation of tetra or penta halo anilines. 2,6-Dibromoaniline may be prepared by brominating sulfanilic acid and subsequently removing the sulfonic group.¹¹⁶ Acetanilide may be iodinated by means of iodine chloride.¹¹⁷

Aniline sulfate may be *nitrated* directly in sulfuric acid solution. Using one equivalent of nitric acid highly diluted with sulfuric acid, and carrying out the reaction in the cold, the three isomeric mononitroaniline sulfates are formed simultaneously, with the meta and para isomers predominating. The meta isomer forms in the greater proportion the higher the concentration of sulfuric acid.¹¹⁸ When the acid solution of the mixture of the three isomeric nitranilines is gradually neutralized, the *ortho* isomer precipitates out first, then the *para* compound, and finally *meta*-nitraniline separates out. *Ortho* and *meta* nitranilines are volatile with steam and may be separated from the *para* isomer by steam distillation.¹¹⁹ On nitrating dimethylaniline in solution in a large volume of

sulfuric acid with a mixture of nitric and sulfuric acids, *meta*-nitrodimethylaniline is formed as the principal product with smaller amounts of the *para* isomer.¹²⁰ When energetically nitrated, dimethylaniline gives dinitro- and tetranitronitrosomethylanilines.¹²¹ Nitroanilines, treated with mixed acids, give nitroaminonitro derivatives.³¹² A nitro group in the *meta* position favors the nitration of the amino group.

When acetanilide in solution in concentrated sulfuric acid is nitrated with the calculated amount of nitric acid at a very low temperature, *para*-nitroacetanilide is formed almost exclusively.¹²² Under other conditions, the *ortho* and *para* isomers are formed simultaneously. Nitration with an equivalent of nitric acid dissolved in a mixture of glacial acetic acid and acetic anhydride results in the formation, largely, of *ortho*-nitroacetanilide.¹²³ The nitro group may be forced into *ortho* position in acetanilide or oxanilide, if a sulfo group is introduced into *para* position prior to nitration and is subsequently removed.¹²⁴ Energetic nitration of acetanilide leads to the formation of 2,4-dinitroacetanilide.

When benzanilide is nitrated with fuming nitric acid without the addition of sulfuric acid, a mixture of *ortho* and *para* nitrobenzanilides is obtained with a small proportion of the *meta* nitro compound.¹²⁵

Benzylidene aniline, $C_6H_5N = CHC_6H_5$, nitrated in sulfuric acid, gives *para*-nitrobenzylidene aniline.¹²⁶

Nitrilanines are formed on heating halonitrobenzenes with alcoholic ammonia at 150–180°, or nitrophenol ethers with aqueous ammonia. *Meta* nitro derivatives do not undergo this reaction.

2,4-Dinitroanilines result through the replacement of a hydrogen atom in *meta* nitro compounds by reaction with alcoholic hydroxylamine.¹²⁷

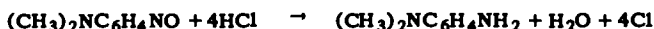
Nitrated aromatic amines result through the partial reduction of aromatic di- or polynitro compounds.¹²⁸ Reduction may be carried out with ammonium sulfide, or with tin or stannous chloride and hydrochloric acid, in alcoholic solution.

Ortho and *para* nitrilanines are converted to the corresponding nitrophenols when boiled with caustic. The *meta* isomer does not undergo this reaction.¹²⁹ Di- and trinitranilines undergo the reaction much more readily. Treated with sodium or potassium alcoholates in warm benzene solution, *para* nitriline gives a colored mono potassium or sodium salt probably having the structure $NH = C_6H_4 = NOOM$, M representing the alkali metal.¹³⁰

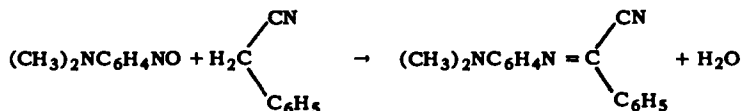
Certain nitrated amines are obtained directly from aromatic amino compounds by the action of anhydrous nitric acid. This is possible, for example, in the anthraquinone series.³¹³

Para nitroso derivatives of secondary aromatic amines are obtained on heating the N-nitroso amines with alcoholic hydrochloric or hydrobromic acid (*Fischer-Hepp transformation*). The nitroso derivatives of these amines result directly from their reaction with nitrous acid. *Para* nitroso derivatives of tertiary aromatic amines are formed when these amines are made to react with nitrous acid.¹³¹ The presence of a substituent in the *para* position prevents reaction. The presence of a substituent in the *ortho* position may also prevent reaction.¹³² Thus, dimethyl-*ortho*-toluidine, $CH_3C_6H_4N(CH_3)_2$, cannot be nitrosated.

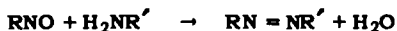
When the *p*-nitroso compounds of tertiary aromatic amines are heated with aqueous caustic, they are decomposed, yielding a sodium para nitro phenolate and an alkyl amine. When heated with concentrated hydrochloric acid, para-nitrosodimethylaniline reacts to form *p*-aminodimethylaniline and aminodichlorodimethylaniline:



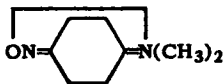
tert-Nitrosoanilines are capable of condensing with compounds containing reactive methylene to form azomethines;¹³³



Aromatic nitroso compounds react with primary aromatic amines to form azo compounds:



p-Nitrosoanilines may be regarded as quinone derivatives,



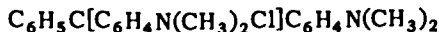
This view is supported by the evidence in regard to the structure of the closely related nitrosophenols.¹³⁴

Aniline is readily *sulfonated* by heating with concentrated sulfuric acid or fuming sulfuric acid of low sulfur trioxide content. *p*-Aminobenzenesulfonic acid, also termed sulfanilic acid, is formed first. Further sulfonation leads to the formation of aniline-2,4-disulfonic acid.¹³⁵

The *para*-standing hydrogen atom in *N*-dialkylated anilines is of high mobility; for this reason these compounds are capable of condensing with aldehydes. Thus, with formaldehyde they give diphenylmethane derivatives of the type



and with benzaldehyde, in the presence of hydrogen chloride they form compounds of the type of leucomalachite green, $\text{C}_6\text{H}_5\text{CH}[\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2]_2$. They react with orthoformic ester in the presence of zinc chloride to give hexaalkylene *p*-leucanilines, such as $\text{CH}[\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2]_3$. Reaction with benzotrichloride results in the formation of compounds of the type of malachite green,¹³⁶



while reaction with phosgene, COCl_2 , in the presence of aluminum chloride results in the formation of compounds of the type of Michler's ketone,¹³⁷



Homologs of N-dialkylated anilines in general react in a similar manner. N-Di-alkyl aryl amines with a free *para* position are converted to N-tetralkyl diamino-diphenyls when oxidized in acid solution with lead peroxide or potassium permanganate.

Behavior and Reactions of Aromatic Amines

The simpler primary aromatic amines can be distilled without decomposition at ordinary pressure. They are slightly soluble in water and are volatile with steam. In contrast to the monoamines, diamino compounds are appreciably soluble in cold water. Amines with an aliphatically bound amino group are more readily soluble in water than purely aromatic amines.

The simpler primary amines are much weaker bases than primary alkyl amines. They do not possess an ammoniacal odor, show no alkaline reaction to litmus and phenolphthalein, and do not combine with carbon dioxide. Their salts react acid. N-Alkylated anilines are also weak bases, and do not react alkaline, but are capable of forming salts with acids. Dimethylaniline gives a mono and dihydrochloride with dry hydrogen chloride. The basic strength of diphenylamine is lower than that of aniline; the compound is capable of forming salts with acids, but these are immediately decomposed by water. Triphenylamine does not combine with acids. The basicity of aromatic amines is decreased when halogen atoms or nitro groups are introduced into the nucleus. The decrease caused by a nitro group is greater than that brought about by a halogen atom. Monohalo derivatives of aniline form salts that are stable in water; salts of dihalo derivatives decompose to a large extent on evaporation of their aqueous solutions, while trihalo derivatives do not form salts with aqueous acids. *Meta*-standing nitro groups exert the least influence on the basicity of aromatic amines, while *ortho*-standing groups exert the greatest effect.¹³⁸ The acidic character of acetanilide is enhanced by nitro groups, and again, the effect of a group at *meta* position is barely perceptible, while *ortho* and *para* nitroacetanilides are sufficiently acidic to dissolve in cold aqueous alkalis.¹³⁹ *Para* diamines form crystalline salts with two equivalents of acid, while *meta* and *ortho* diamines in general combine with one equivalent of acid. Triaryl amines combine with an atom of halogen forming salts in which the cation is a free radical, $\{\text{Ar}_3\text{N}\}^+$. Aromatic amines with an aliphatically bound amino group possess an ammoniacal odor, and show an alkaline reaction. They combine readily with carbon dioxide of the air. Such amines do not form diazo compounds with nitrous acid, but are converted by this reagent to the corresponding alcohols. They combine with carbon disulfide giving the amine salts of dithiocarbamic acids.

The reaction of primary aromatic amines or their salts with nitrous acid results in the formation of *diazo compounds*. These compounds have played an extremely important role in the development of organic chemistry, because of a high reactivity which made possible their conversion into a great variety of products of substitution. They are also of great importance in the dye industry. They are dealt with in Chapter 17.

The mobility of the amino group in aromatic amines is influenced by substit-

uents in the nucleus. Aniline and its homologs may be boiled with aqueous alkalis and acids without loss of the amino group. *p*-Nitrosoaniline, on the other hand is converted to *p*-nitrosophenol by boiling with aqueous alkalis.³¹⁴ Nitro groups in *ortho* or *para* position also affect the mobility of the amino group. 2,4-Dinitro- and 2,4,6-trinitroanilines are converted to the corresponding dinitro- and trinitrophenols by boiling with aqueous alkalis.³¹⁵ *Naphthylamines* are converted to naphthols by heating with aqueous acids or alkalis.³¹⁶ Hydrolysis in this instance may be effected readily by heating with aqueous solutions of sodium bisulfite.³¹⁷

Aromatic amines may be alkylated by heating with an alkyl halide, preferably the iodide or bromide; or by heating with an alcohol in an autoclave in the presence of an acid. The reaction is generally reversible, and an alkyl halide and a primary aromatic amine result on heating N-alkylated aromatic amines with a hydrogen halide. Heated with chloroform and aqueous alkali, primary aromatic amines yield isonitriles. Alkali metals dissolve in amines on heating with liberation of hydrogen, giving mono- and dialkali metal derivatives, which, however, have not been isolated in the free state.

Acylation of Aromatic Amines and Related Reactions

Anilides, ArNHCOAlk , may be obtained by methods employed for the preparation of aliphatic amides. They may be obtained by heating the fatty acid salts of primary aromatic amines; through the reaction of amines with aliphatic esters, acid halides or anhydrides; and by the interaction of aliphatic esters with halo-magnesium compounds of the amines, ArNHMgX .

Acetanilide is formed when aniline is boiled with glacial acetic acid.¹⁴⁰ The reaction of aromatic amines with thioacetic acid, CH_3COSH , is found to be very satisfactory for the preparation of acylated amines.¹⁴¹ N-Monoalkylated amines may be acylated by reaction with acid halides or anhydrides.

Diacetanilide, $\text{C}_6\text{H}_5\text{N}(\text{COCH}_3)_2$, results when acetanilide is heated at $170\text{--}180^\circ$ with acetyl chloride, or at $200\text{--}205^\circ$ with acetic anhydride.¹⁴² It may be obtained directly from aniline by heating with an excess of acetic anhydride. The compound isomerizes to *p*-acetaminoacetophenone, $\text{CH}_3\text{CONHC}_6\text{H}_4\text{COCH}_3$.¹⁴³

Oxanilic acid, $\text{C}_6\text{H}_5\text{NHCOCOOH}$, results on heating aniline at $130\text{--}140^\circ$ with slightly more than one molecular equivalent of anhydrous oxalic acid. *Oxanilide*,



results when oxanilic acid is heated at $160\text{--}180^\circ$. Oxanilic acid is converted to phenylisocyanate when it is heated with phosphorus pentachloride.

Formyldiphenylamine, $(\text{C}_6\text{H}_5)_2\text{NCHO}$, results when diphenylamine is heated at 100° with concentrated formic acid. The reaction fails to proceed with dilute formic acid. Acetyldiphenylamine, $(\text{C}_6\text{H}_5)_2\text{NCOCH}_3$, is obtained by heating diphenylamine with acetic anhydride.

Acetyl bromide reacting with dimethylaniline gives acetylmonomethylaniline,

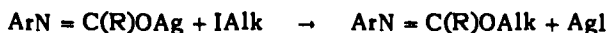


similarly, benzoyl bromide gives benzoylmonomethylaniline.¹⁴⁴

The free aminosulfonic acids, which are in reality inner sulfonic salts, cannot be acetylated with acetic anhydride. The sodium salts of these amines are readily acetylated, however, by this reagent.¹⁴⁵

Anilides are stable compounds, and many can be distilled without decomposition. They can be halogenated and nitrated directly. When heated with alkalis or with hydrochloric acid, they are decomposed into the original amine and the alkali metal salt of the acid, or the acid itself. When boiled with sulfur they are converted into benzothiazoles.

Anilides react with sodium hydroxide to form sodio derivatives $\text{ArN}=\text{C}(\text{ONa})\text{R}$; these compounds react with alkyl iodides to give N-alkyl anilides. The silver compounds of anilides are obtained by shaking the anilide with silver oxide. These silver compounds, reacting with alkyl iodides, give O-alkyl derivatives:

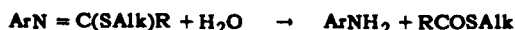


Methylation of anilides by heating with dimethyl sulfate results in the formation of the O-methylated derivatives.¹⁴⁶

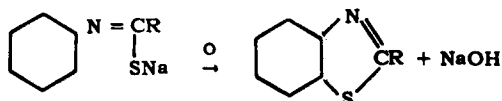
The hydrogen attached to the nitrogen atom in anilides may be replaced with a chlorine or bromine atom by the action of sodium hypochlorite or hypobromite. The N-halo anilides readily undergo rearrangement to nuclearily halogenated anilides. The rearrangement is promoted by hydrogen chloride or by sunlight.¹⁴⁷

Thioanilides¹⁴⁸ are formed on melting a mixture of the anilide with phosphorus pentasulfide. The thioanilide is isolated by dissolving the crude reaction product in dilute caustic, and precipitating the thioanilide by conducting a current of carbon dioxide through the solution.

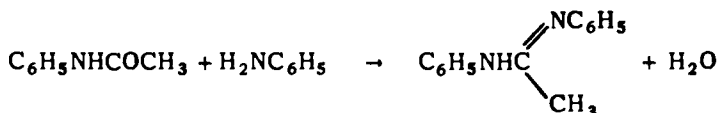
In contrast with their oxygen analogs, thioanilides are distinctly acidic in character, and dissolve readily in dilute alkalis to form stable salts. The free thioanilides are precipitated from the solution of their alkali metal salts with carbon dioxide. The alkali metal in these salts is attached to sulfur, $\text{ArN}=\text{C}(\text{SNa})\text{R}$, and reaction with alkyl halides consequently leads to the formation of S-alkylated derivatives. The S-alkylated derivatives are converted to esters of thio acids on hydrolysis with dilute hydrochloric acid:



On oxidation of the alkali metal salts in aqueous solution with potassium permanganate, benzothiazole derivatives are formed:¹⁴⁹



Phenylated amidines are formed on heating a mixture of aniline hydrochloride and an anilide, or one of aniline, an anilide, and phosphorus trichloride:¹⁵⁰



These compounds are weak bases that combine with one equivalent of hydrochloric acid.

Diphenylformamidine, $C_6H_5NHCH = NC_6H_5$, reacts with compounds containing reactive methylene with elimination of aniline to form derivatives of formanilide. With malonic ester, for example, the compound $C_6H_5NHCH = C(COOC_2H_5)_2$ is formed.¹⁵¹

The nitration of aniline with nitrogen pentoxide in ethereal solution at -20° ,¹⁵² or with nitric acid in solution in acetic acid, leads to the formation of phenylnitranilide $C_6H_5NHNO_2$. The compound is formed also through the reaction of aniline in ethereal or ethereal-alcoholic solution with ethyl nitrate in the presence of potassium ethoxide;¹⁵³ or by the removal of elements of water from aniline nitrate with acetic anhydride.¹⁵⁴ In the latter method, it is often desirable to moderate the reaction by the addition of glacial acetic acid. Oxidation of benzene *n*- or isodiazotate with potassium ferricyanide or potassium permanganate also leads to the formation of phenylnitranilide, together with the isomeric nitrosophenylhydroxylamine, $C_6H_5N(NO)OH$.¹⁵⁵ In preparing the compound by the last method, it is best to isolate the potassium salt of the nitrosamine, and to oxidize this with potassium ferricyanide.

Phenylnitranilide rapidly undergoes molecular rearrangement to *o*- and *p*-nitroaniline under the action of mineral acids or light. It is stable, however, toward alkalies, and may be boiled with aqueous caustic for a day without undergoing any change.

Secondary and tertiary arylamines of the type of methyl- and ethylaniline and diethylaniline yield monoalkyl nitramines with fuming nitric acid.³¹⁸ Nuclear nitration takes place simultaneously during the reaction.

Primary aromatic amines, treated with an equivalent of nitrous acid in the absence of a mineral acid, give isodiazoo compounds. They form diazonium salts in the presence of acids.

Nitroso Amines; the Fischer-Hepp Transformation

Secondary aromatic amines form nitroso amines by reaction with nitrous acid:




Nitroso amines thus derived from secondary amines are converted to *p*-nitroso amines under the influence of alcoholic hydrochloric acid. This rearrangement, which is known as the *Fischer-Hepp transformation*, involves the exchange of the nitroso group for the para hydrogen in the aromatic nucleus:³⁰⁸



The rearrangement takes place also under the action of alcoholic hydrobromic acid, but not with alcoholic sulfuric acid.

Reaction with Inorganic Acid Chlorides and Carbon Disulfide

Phenylsulfamic acid, $C_6H_5NHSO_3H$, is obtained through the reaction of aniline with chlorosulfonic acid in chloroform solution.¹⁵⁶ This compound is also formed through the reaction of aniline with sulfur trioxide; through the combination of *N*-phenylhydroxylamine with sulfur dioxide; or by heating aniline with an aminosulfonic acid.¹⁵⁷

Sulfimido compounds, such as sulfimidobenzene, C_6H_4 , are obtained by the action

of hydriodic acid on the chlorides of nitrosulfonic acids. They are, in general, indifferent bodies, very stable toward both acids and alkalies.¹⁵⁸

Primary aromatic amines reacting with thionyl chloride, SOCl_2 , give *thionylamines*, $\text{ArN} = \text{SO}$.¹⁵⁹

The reaction of phosphorus trichloride with primary amine hydrochlorides results in the formation of *phosphazobenzene* chloride derivatives, $\text{ArN} = \text{PCl}_2$.¹⁶⁰ The chlorine in these compounds is replaceable with the groups NHC_6H_5 , OC_2H_5 , etc. by heating with $\text{H}_2\text{NC}_6\text{H}_5$, NaOC_2H_5 , etc.

Phosphorus oxychloride, POCl_3 , reacting with aniline hydrochloride, gives *anilido phosphoric dichloride*, $\text{C}_6\text{H}_5\text{NHPOCl}_2$, while reaction with aniline results in the formation of *oxyphosphazobenzene anilide*, $\text{C}_6\text{H}_5\text{NHPO} = \text{NC}_6\text{H}_5$.

Trichlorophosphanil, $\text{C}_6\text{H}_5\text{N} = \text{PCl}_3$, is formed through the reaction of aniline with phosphorus pentachloride.¹⁶¹

Thiophosphazobenzene chloride, $(\text{C}_6\text{H}_5\text{N} = \text{PSCl}_2)_2$, results from the reaction of phosphorus sulfochloride, PSCl_3 , with aniline hydrochloride.¹⁶²

Araenophenylamines are obtained through the reaction of arsenic trichloride or tribromide with aniline in ethereal or chloroform solution.

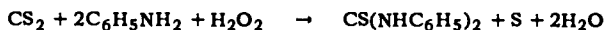
Silicotetraphenylamide, $\text{Si}(\text{NHC}_6\text{H}_5)_4$, results from the reaction of silicon tetrachloride with aniline in benzene solution.¹⁶³

Aromatic ureas are formed through the reaction of aromatic amines with phosgene or chloroformamide.

Aromatic amines heated with carbon disulfide, give symmetrical thioureas:



Diphenylthiourea may be prepared by refluxing a mixture in equal weights of aniline, carbon disulfide and absolute alcohol until the evolution of hydrogen sulfide ceases.³¹⁹ Alternatively, two molecular equivalents of aniline and one of carbon disulfide are refluxed with one molecular equivalent of hydrogen peroxide:³²⁰

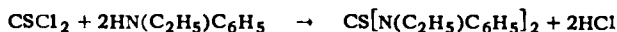


Another method consists in heating a mixture of 4 parts carbon disulfide, 5 parts aniline and 8 parts water with good stirring, until hydrogen sulfide ceases to be evolved.³²¹ This would appear to be the best method for the preparation diphenylthiourea.

The formation of thioureas through the reaction of aromatic amines with carbon disulfide stands in contrast with the behavior of aliphatic amines, which yield dithiocarbamates. Phenylidithiocarbamic acid may be obtained, however, in the form of its alkali metal salt, through the reaction of aniline and carbon disulfide in alcoholic solution in the presence of caustic:¹⁶⁴

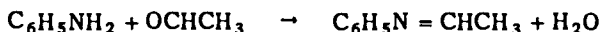


Monophenylthiourea, $\text{C}_6\text{H}_5\text{NHCSNH}_2$, is obtained by the reaction of phenyl isothiocyanate with ammonia, or through the interaction of ammonium thiocyanate and aniline hydrochloride. Unsymmetrical disubstituted thioureas may be prepared through the reaction of secondary aromatic amines with thiophosgene:³²²



Reaction of Aromatic Amines with Aldehydes; Schiff Bases

Aromatic amines react very readily with aliphatic aldehydes with elimination of water to form alkylidine amines:

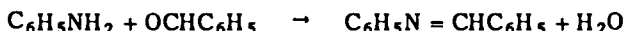


These compounds are very unstable, however, and readily polymerize to crystalline bodies. These appear to be tertiary bases in many instances. Methylidene aniline, $\text{C}_6\text{H}_5\text{N} = \text{CH}_2$, product of the reaction of aniline and formaldehyde,

appears in the trimeric form, $\text{C}_6\text{H}_5\text{NCH}_2\text{N}(\text{C}_6\text{H}_5)\text{CH}_2\text{NC}_6\text{H}_5\text{CH}_2$, known as anhydroformaldehyde aniline. The product resulting from the reaction of aniline with acetaldehyde gives a dimeric body, $\text{C}_6\text{H}_5\text{N} = \text{CHCH}_2\text{CH}(\text{CH}_3)\text{NHC}_6\text{H}_5$, which exists in two isomeric modifications. Dimers are obtained also from other alkylidene anilines. These dimeric products have been converted to derivatives of quinoline bases by heating with acids.

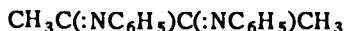
The reaction of aromatic amines with aliphatic aldehydes gives rise readily to compounds in which two amino groups are combined with the alkyl residue.¹⁶⁵ Formaldehyde, for example, reacting with aniline in the presence of alcoholic potassium hydroxide, gives methylenediphenyldiamine, $\text{C}_6\text{H}_5\text{NHCH}_2\text{NHC}_6\text{H}_5$. When heated with aniline hydrochloride, this compound is converted to *p,p*-diaminodiphenylmethane, $\text{H}_2\text{NC}_6\text{H}_4\text{CH}_2\text{C}_6\text{H}_4\text{NH}_2$.

The reaction of aromatic amines with aromatic aldehydes proceeds in a simple manner, one equivalent of amine combining with one of aldehyde with elimination of water:



The resulting compounds are known as *Schiff bases*.

The carbonyl group in ketones is far less reactive than that in aldehydes, although condensation products of the type $\text{ArN} = \text{CRR}'$, called *anils*, have been obtained with certain ketones. Diacetyl gives a dianil,



with aniline quite readily. This dianil is rapidly decomposed by acids to the original diketone and aniline.

Quaternary Ammonium Bases from Tertiary Aromatic Amines

Many tertiary alkyl aromatic amines combine with alkyl halides to form salts of quaternary ammonium bases.¹⁶⁶ For example, dimethylaniline reacts energetically with methyl iodide, forming trimethylphenylammonium iodide,



Substituents in the ortho position in the aromatic nucleus hamper or even prevent the formation of quaternary bases.¹⁶⁷ Salts of such quaternary bases are crystalline bodies, which are not decomposed by cold aqueous alkalis. The free bases can be liberated, however, by treating their halides with moist silver oxide.

Aromatic quaternary ammonium halides can be smoothly converted to the tertiary amines by boiling with sodium ethoxide.¹⁶⁸ Trimethylphenylammonium iodide is decomposed into dimethylaniline and methyl iodide when distilled in

a current of hydrogen chloride. Prolonged boiling with concentrated aqueous potassium hydroxide causes the decomposition of the quaternary iodide to dimethylaniline and methanol.

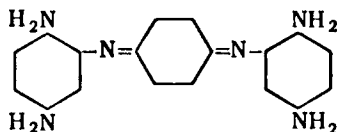
Some of the quaternary ammonium halides have been resolved into optical isomers by fractional crystallization of their bromocamphorsulfonates.¹⁶⁹ The pure isomers gradually lose their activity in solution, especially in solvents containing hydroxyl groups.

Oxidation of Aromatic Amines

Aromatic amines are susceptible to oxidation, and depending upon the nature of the amine and upon the experimental conditions, diverse compounds result. Primary aromatic amines are smoothly oxidized to nitroso compounds by Caro's acid, HOSO_2OOH .¹⁷⁰ Peracetic acid and aqueous sodium peroxide also bring about this oxidation.¹⁷¹ Primary amines may be oxidized to azo compounds; thus aniline, treated with alkaline permanganate, gives azobenzene, $\text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_5$, together with a little ammonia and oxalic acid. The free *p*-toluidines are readily oxidized to azo compounds.¹⁷² More vigorous oxidation, for example by use of chromic acid mixture, converts aniline largely to quinone. Oxidation of aniline with hydrogen peroxide in acetic acid solution results in the formation of dianilidoquinone anilide, $\text{C}_6\text{H}_5\text{N}=\text{C}_6\text{H}_2\text{O}(\text{NHC}_6\text{H}_5)_2$. *p*-Quinones may be obtained also from *o*- and *m*-toluidines and from *p*-xylydine by oxidation with chromic acid.¹⁷³ Some amines with a methyl group in the *para* position with respect to the amino group, such as mesidine and ψ -cumidine, are converted to quinones on oxidation, with removal of a methyl group.¹⁷⁴ A very dark colored substance is first formed when aniline is oxidized with chromic acid. This substance, known as *aniline black*, is formed also by the oxidation of aniline with other agents,¹⁷⁵ and by electrolysis.

Diamino compounds are especially sensitive toward oxidizing agents. The free bases in aqueous solution undergo spontaneous oxidation in contact with atmospheric oxygen, although the solid bases and their salts in the dry condition can be kept unchanged. *p*-Quinones are formed when *p*-diamines are oxidized with manganese dioxide and sulfuric acid, or with sodium dichromate and sulfuric acid. Quinoid compounds of the type $\text{HN}=\text{C}_6\text{H}_4=\text{NH}$ result when the oxidation is carried out under milder conditions; for example, when the compound in ethereal solution is shaken with silver oxide.

Oxidation of *p*-phenylenediamine in aqueous ammoniacal solution with potassium ferricyanide or with oxygen results in the formation of a quinoid complex known as Bandrowski's base,¹⁷⁶



Dialkylanilines are oxidized by hydrogen peroxide or permonosulfuric acid to dialkylaniline oxides.¹⁷⁷ Dimethylaniline, for example, is converted to dimethylaniline oxide, $\text{C}_6\text{H}_5\text{N}(\text{O})(\text{CH}_3)_2$.

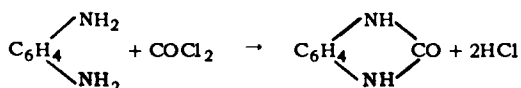
The side chain in homologs of aniline may be successfully oxidized to a carboxyl group, providing the amino group is protected by acetylation.¹⁷⁸ Thus, acetotoluidines, $\text{CH}_3\text{C}_6\text{H}_4\text{NHCOCH}_3$, may be converted to acetaminobenzoic acids, $\text{HOCOC}_6\text{H}_4\text{NHCOCH}_3$, by oxidation with potassium permanganate.

N-Dialkylanilines with a free *para* position are converted to N-tetraalkyl-diaminodiphenyl derivatives when oxidized with lead peroxide or acid potassium permanganate.

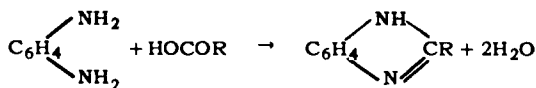
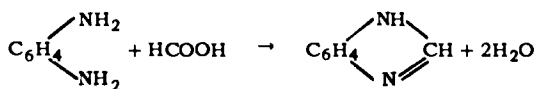
Amines show great resistance to *reducing agents*. They may be hydrogenated, however, by passing their vapors mixed with hydrogen over finely divided nickel at 190° . Catalytic reduction in the presence of metallic nickel can be successfully carried out also under pressure. Cyclohexylamine can be prepared in this manner from aniline.¹⁷⁹

Reactions of o-Diamino Compounds Resulting in Ring Closure

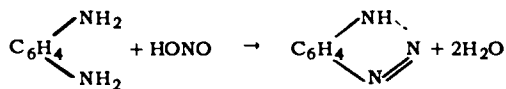
Ring closure takes place with *ortho* diamines when more than one reactive bond is available in the compound reacting with the diamine. Phosgene, for example, reacts with o-diamines to form a cyclic urea:



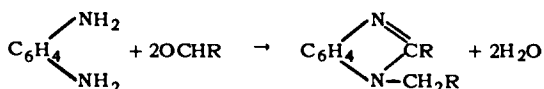
Condensation with formic acid or other aliphatic acids results in the formation of imidazoles:¹⁸⁰



With nitrous acid, azimides are formed:¹⁸¹

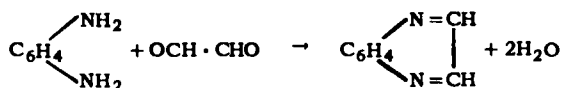


The reaction with aldehydes is characteristic and leads to the formation of aldehydines:¹⁸²



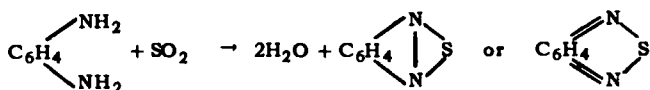
This is known as *Ladenburg's reaction*. Aldehydines are strongly basic in character and are not decomposed when boiled with dilute acids. Their hydrochlorides result when aldehydes are made to react with the hydrochloride of the *ortho* diamine.

The reaction of glyoxal and 1,2-diketones with o-diamines results in the formation of glyoxalines:

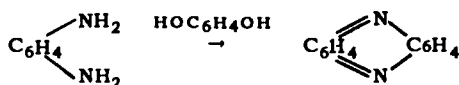


The reaction generally proceeds with extreme ease and is of preparative importance. *Phenanthraquinone* is capable of undergoing this reaction in boiling glacial acetic acid, forming phenanthrazenes, which usually precipitate out of solution. The reaction may be employed for the identification of *o*-diamines.

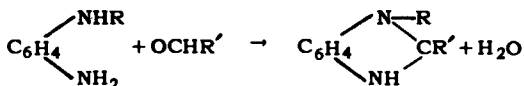
Ortho diamines react with sulfur dioxide to form *piazthiols*:



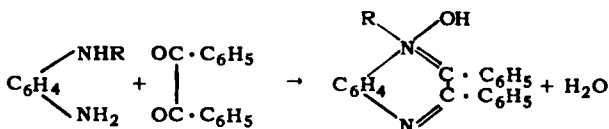
Reaction with catechin results in the formation of a phenazine:



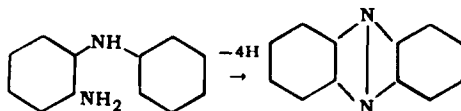
Ring formation also takes place with *ortho* semidines reacting with certain compounds. With aldehydes they yield compounds probably corresponding to hydroimidazoles:



With 1,2-diketones they form azonium bases characterized by strong basicity and fluorescence:



o-Semidines react with nitrous acid to form azimides; they react with acids to form basic anhydro compounds. When distilled with lead oxide, *o*-semidines are converted to azines:



Quinolines may be synthesized by heating aromatic bases with glycerol, sulfuric acid, and nitrobenzene. This reaction is known as the Skraup quinoline syntheses.

Primary aromatic amines heated with α -halo ketones give *indoles* or, occasionally, dihydropyridine derivatives.

AROMATIC HYDROXYLAMINES, HYDRAZINES AND RELATED COMPOUNDS

Preparation of Hydroxylamines

Aromatic hydroxylamines, ArNHOH , may be obtained through the partial reduction of aromatic nitro compounds. They are formed when aromatic nitro compounds are boiled in aqueous alkaline solution with zinc dust.¹⁸³ The reaction is greatly accelerated by the addition of ammonium-, calcium-, or magnesium chlorides, and the presence of a little ether is often beneficial.

Success of this reaction depends on the quality of the zinc dust and the temperature. Zinc dust coppered by stirring with a small amount of saturated copper sulfate solution is claimed to give satisfactory results. Four parts of copper sulfate are used to 100 parts of zinc dust.

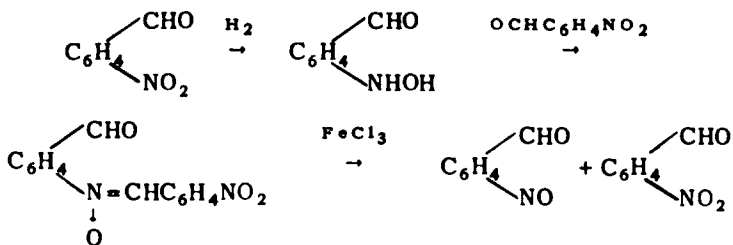
The reduction of aromatic nitro compounds to the corresponding hydroxylamines may be simply and satisfactorily effected with ammonium sulfide in the cold.¹⁸⁴ Nitrobenzene and its halo derivatives may be reduced to the corresponding hydroxylamines with sodium hydrogen sulfide.¹⁸⁵

Other reducing agents also convert nitro compounds to hydroxylamines. Thus, alkaline stannous chloride solutions are suitable for the reduction of nitroanthraquinones.¹⁸⁶ Other methods involve the use of sodium amalgam and moist ether,¹⁸⁷ and zinc amalgam.¹⁸⁸

Hydroxylamines result in good yield when nitro compounds are catalytically reduced with hydrogen in neutral solution in the presence of palladized animal charcoal. The nitro compounds are dissolved in alcohol and shaken with hydrogen at ordinary pressure in the presence of the catalyst until the calculated quantity of hydrogen has been absorbed. In alkaline solution, in a limited range of alkalinity, hydrazobenzenes are obtained by this method.¹⁸⁹

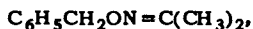
Hydroxylamines are formed when aromatic nitro compounds are reduced electrolytically in neutral solution.¹⁹⁰ Reduction in acid solution results in the formation of *p*-aminophenol due to a molecular rearrangement.¹⁹¹

Nitrobenzaldehydes have been reduced electrolytically to hydroxylamines, which however rapidly underwent condensation with unconverted nitro aldehyde, yielding nitrones.³²³ The latter are readily oxidized with ferric chloride to nitro and nitrosobenzaldehydes:



These methods are not entirely satisfactory for the conversion of dinitro compounds, nitramines, and nitrophenols to the corresponding hydroxylamines.¹⁹²

The reaction of benzyl chloride or bromine with hydroxylamine results in the formation of β -dibenzylhydroxylamine, $(C_6H_5CH_2)_2NOH$. Further benzylation results in the formation of tribenzylhydroxylamine, $(C_6H_5CH_2)_2NOCH_2C_6H_5$, a compound which is also formed through the reaction of benzyl chloride or bromide with α -benzylhydroxylamine, $H_2NOCH_2C_6H_5$. The latter is formed when benzylacetoxime,



is hydrolyzed. Benzylacetoxime, in turn, is obtained from the sodio compound of acetoxime by reaction with benzyl chloride.¹⁹³ α,β -Dibenzylhydroxylamine,



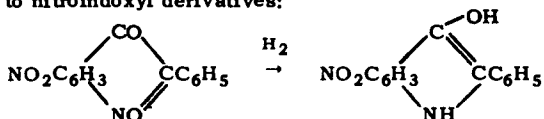
is obtained through the partial benzylation of α -benzylhydroxylamine with benzyl chloride.

β -Benzylhydroxylamine, $C_6H_5CH_2NHOH$, is obtained when α,β -dibenzylhydroxylamine is hydrolyzed with concentrated hydrochloric acid. Hydrolysis of benzyliisobenzaldoxime,



by the same method also gives β -benzylhydroxylamine. It has not been possible to separate this compound into optical isomers.

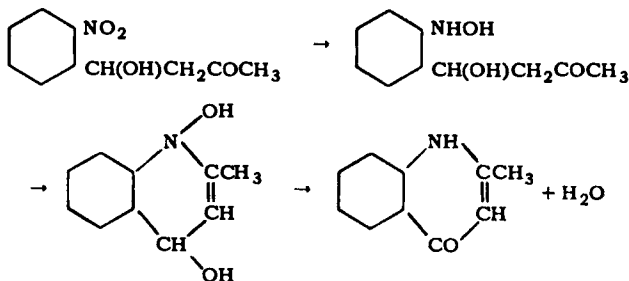
Nitroisatogens are reduced by stannous chloride and glacial acetic acid, or with phenylhydrazine to nitroindoxyl derivatives:



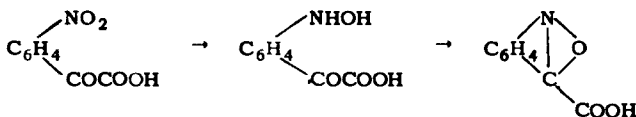
All similar N-oxy compounds are reduced to indoxyl derivatives with zinc dust and glacial acetic acid.¹⁹⁴

Ring Formation Resulting from Reduction of Certain Nitro Compounds

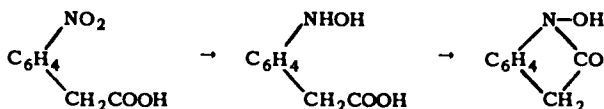
Aromatic nitro compounds containing an *ortho* substituent with a keto or carboxyl group may undergo cyclization when reduced. β -o-Nitrophenyl- β -hydroxy ethyl methyl ketone, reduced with zinc dust and acetic acid, gives γ -ketohydroquinaldine:¹⁹⁵



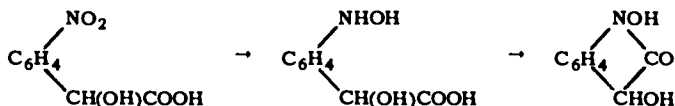
o-Nitrophenylglyoxylic acid is converted to anthroxantic acid by reduction with zinc dust in ammoniacal solution:¹⁹⁶



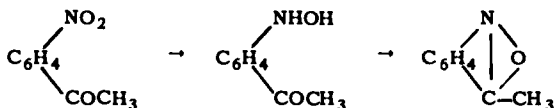
o-Nitrophenylacetic acid gives a hydroxylamine derivative when reduced with zinc dust and sulfuric acid; an inner acylation converts this to 1,2-dioxindole:¹⁹⁷



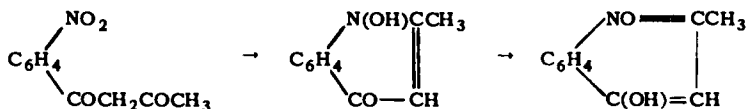
Similarly *o*-nitromandelic acid gives *N*-hydroxydioxindole when reduced with zinc dust in ammoniacal solution:¹⁹⁸



o-Nitroacetophenone, reduced with tin and glacial acetic acid, gives methylantranil:¹⁹⁹



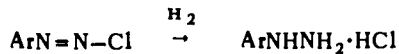
Hydroxyquinaldine oxide is obtained when *o*-nitrobenzoylacetone is treated with hydriodic acid and phosphorus:²⁰⁰



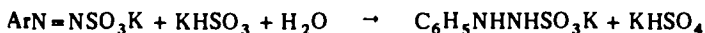
Phenylhydroxylamine is converted by nitrous acid into phenylnitrosohydroxylamine, $\text{C}_6\text{H}_5\text{N(NO)OH}$, a compound which does not reduce Fehling's solution even on boiling, and is very stable toward alkalis. It forms alkali metal salts which react neutral and are not decomposed by carbon dioxide.

Preparation of Aromatic Hydrazines³²⁴

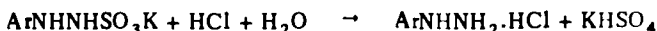
Aromatic hydrazines are obtained by the reduction of aromatic diazo compounds:



Sulfurous acid or an alkali hydrosulfite are the reducing agents most commonly used. The first stage of the reaction is the formation of a diazo sulfonate when an alkali metal hydrosulfite is used as the reducing agent.²⁰¹ This is reduced to a hydrazinesulfonate:



The hydrazine chloride is formed when the sulfonate is heated with concentrated hydrochloric acid:²⁰²



Conversion of *p*-nitrophenyldiazonium chloride to the corresponding hydrazine is best effected by this method.²⁰³ Ammonium hydrosulfite may be employed in the reaction instead of the alkali metal bisulfite.²⁰⁴ In the reduction of anthraquinone- α - and β -diazonium sulfates, the diazosulfonate forms as a distinct compound. The method has been adopted as the standard practice for the commercial production of aromatic hydrazines.

Diazonium salts are directly reduced to hydrazine salts with stannous chloride and hydrochloric acid below 0°:²⁰⁵



This is a convenient method for the preparation of hydrazines in the laboratory. The method is applicable to *p*-nitrobenzenediazonium chloride, benzene-*o*-tetrazonium chloride, and the diazonium compounds of the anthraquinone series.

Reduction of diazonium salts to hydrazines may also be brought about by use of zinc dust and acetic acid. Diazoamino compounds give a hydrazine and an amine when reduced in alcoholic solution with zinc dust and acetic acid. Hydrazines are also formed when alkali metal salts of diazo- and isodiazo-benzene are reduced with sodium amalgam.²⁰⁶

Diazonium salts have been converted to hydrazines by electrolytic reduction.³⁴⁰

N-Alkylated aromatic hydrazines are obtained through the reaction of alkyl bromides with an aromatic hydrazines.²⁰⁷ Both α - and β -alkylhydrazines are formed in this reaction, the α -isomer predominating. The β -compounds are converted to azo compounds on oxidation with mercuric oxide, and can be isolated as such by steam distillation, since the azo compounds are volatile with steam. The azo compounds can be reconverted to the hydrazines by reduction. α -Alkylated aromatic hydrazines are formed through the reaction of alkyl bromides with sodio arylhydrazines,²⁰⁸ or by reducing the nitroso derivative of secondary aromatic aliphatic amines.²⁰⁹ α -Alkylated aryl hydrazines are also obtained when β -acetohydrazines are made to react with alkyl halides and the resulting products are hydrolyzed by boiling with an aqueous mineral acid.²¹⁰ The solubility of the hydrochloride of α -alkyl phenylhydrazines in benzene or ether may be utilized for the separation of these compounds from primary hydrazines and secondary aniline bases.²¹¹ β -Alkylarylhydrazines are formed by the reduction of arylhydrazones of aliphatic aldehydes and ketones. *Dialkyl phenylhydrazines* may be obtained from the sodio derivative of α -alkyl phenylformylhydrazines, $\text{C}_6\text{H}_5\text{N}(\text{Alk})\text{N}(\text{Na})\text{CHO}$, by reaction with alkyl iodides and subsequent removal of the formyl group by treatment with concentrated hydrochloric acid. α - β -Dimethyl- and α , β -diethylphenylhydrazines are formed by the action of zinc dimethyl or zinc diethyl on benzenediazonium chloride.²¹²

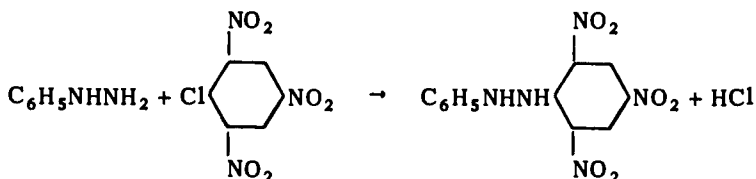
Symmetrical *diaryl hydrazines*, ArNHNHAr , the so-called hydrazo compounds, are formed by the careful reduction of the corresponding azo compounds,



Reduction of an azo compound to a hydrazo compound may be brought about by boiling an alkaline alcoholic solution of the azo compound with zinc dust.²¹³ Reduction may be effected also with alcoholic ammonium sulfide or sodium disulfide,²¹⁴ by heating with iron powder and caustic solution, or with aluminum amalgam.²¹⁵ Other reducing agents which have been used for the purpose are sodium amalgam, ethylmagnesium bromide, zinc dust and glacial acetic acid,²¹⁶ and phenylhydrazine heated at 160-170°.²¹⁷ Sodium amylate has also been employed for the purpose.²¹⁸ The reduction has been effected electrolytically.³⁴¹

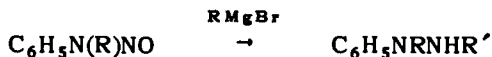
Hydrazo compounds may be prepared directly from nitro compounds by reduction with zinc dust in alkaline alcoholic solution.²¹⁹ This method is of technical importance. Electrolytic reduction of nitro compounds to hydrazo compounds has also been accomplished.²²⁰ The reduction has been carried out in aqueous alkali, in the presence of finely divided metallic lead or lead compounds.

Nitrated hydrazo compounds may be obtained through the reaction of halo-nitro compounds with hydrazines:²²¹



The reaction of hydrazine with di- and trinitrophenol ethers gives hydrazines through an exchange of the alkoxy group of the ether for the hydrazino group.³⁴²

The only method of any value for the preparation of tri-substituted hydrazines is the reaction of Grignard compounds with nitrosamines:²²²



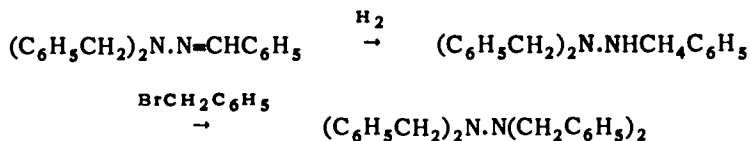
Tetraaryl hydrazines have been made by the action of iodine on the sodio derivatives of diaryl amines.²²³



They are more conveniently prepared by the oxidation of diarylamines in etheral or benzene solution with lead peroxide, or in acetone solution with potassium permanganate:²²⁴



Dialkyldiarylhydrazines, ArN(Alk)N(Alk)Ar , may be obtained from the corresponding tetrazenes, $\text{ArN(Alk)N=N.N(Alk)Ar}$, by heating to 120-140°.³⁴² Tetra-benzylhydrazine, $(\text{C}_6\text{H}_5\text{CH}_2)_2\text{N.N(CH}_2\text{C}_6\text{H}_5)_2$, has been made by reducing benzylidenedibenzylhydrazine and treating the resulting tribenzylhydrazine with benzyl bromide:



Properties and Reactions of Aromatic Hydrazines

Aromatic hydrazines are sparingly soluble in water, but are freely soluble in alcohol and in ether. In contrast with aliphatic hydrazines, the aromatic hydrazines combine with only one equivalent of acid. This is true also of secondary hydrazines, the salts of which are partially decomposed with water. Hydrazo compounds, $\text{ArNH}\cdot\text{NHAr}$, are neutral in character, providing they do not contain basic or acidic groups. The hydrogen of the imide group in hydrazines is replaceable with alkali metals.²²⁵ Primary aromatic hydrazines reduce Fehlings solution in the cold, while the secondary hydrazines reduce the solution only on heating. When heated strongly, hydrazo compounds are converted in part to azo compounds, in part to an amine:²²⁶

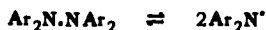


These compounds cannot, therefore, be distilled unchanged.

Metallic sodium dissolves readily in phenylhydrazine when heated with the latter, forming the sodio derivative of phenylhydrazine, $\text{C}_6\text{H}_5\text{N}(\text{Na})\text{NH}_2$. A portion of the phenylhydrazine is decomposed in the process into aniline and ammonia. The sodio derivative may be isolated by distilling off the volatile components of the reaction mixture. The compound reacts with atmospheric moisture and should be protected by a layer of anhydrous ether or benzene.

Tetraaryl hydrazines are crystalline solids which can be kept intact in the dark, but decompose rather rapidly in solution. They are not basic in character.

Tetraaryl hydrazines dissociate spontaneously in solution into free radicals which contain a divalent nitrogen:²²⁷



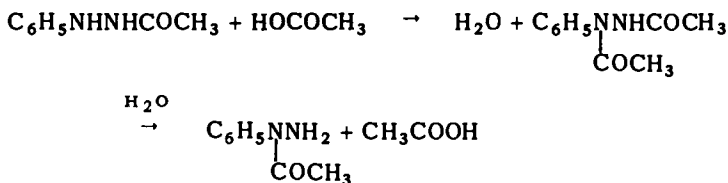
The aromatic nuclei must be attached directly to the nitrogen atom in order that dissociation into radicals should occur. Tetrabenzylhydrazine, for example, fails to dissociate in solution, and is otherwise stable. It is of interest to note that while tetra-(dimethylaminophenyl)-hydrazine is largely dissociated in solution, its salts are not thus dissociated.

Tetraaryl hydrazines do not form salts with acids but are capable of combining with halogens to form salts of the type $[\text{Ar}_2\text{N}\cdot\text{NAr}_2]\text{X}$. When such a salt in neutral solution is treated with potassium iodide, iodine is liberated immediately and the original tetraarylhydrazine regenerated.

Aromatic hydrazines may be *acylated* through the reaction of the free hydrazine with acids. The primary amino group in the hydrazine is the first point attacked:²²⁸



Many acids react so readily that it is sufficient to heat them with an aqueous solution of the hydrazine acetate to obtain the hydrazide. This is particularly true of the oxygen-rich acids of the sugar series, and the reaction is utilized for the isolation of these sugar acids.²²⁹ Aromatic hydrazides may be obtained through the reaction of acid halides or acid anhydrides with the free hydrazines. Acid anhydrides reacting with hydrazo compounds, ArNH.NHAr , give diacylated derivatives.²³⁰ Malonimide heated at 200° with phenylhydrazine gives malonyl diphenylhydrazide.²³¹ Unsymmetrical acyl hydrazides may be prepared from the symmetrical by further acylating the symmetrical compound, then boiling the resulting diacyl hydrazide with a mineral acid:²³²



The α -acyl compound may also be prepared by treating the sodio derivative of the hydrazine with an acid halide or anhydride,²³³ or by treating a cold benzene solution of an N-chloroanilide, RCONClAr, with finely divided sodium amide.²³⁴

Malonyl monophenylhydrazide, $\text{HOCOCH}_2\text{CONHC}_6\text{H}_5$, is converted to malonyl phenylhydrazide, $\text{COCH}_2\text{CONHC}_6\text{H}_5$, when heated; succinyl iminophenylhydrazide gives succinophenylhydrazil, $\text{COCH}_2\text{CH}_2\text{CONHC}_6\text{H}_5$. Maleic acid reacting with phenylhydrazine gives 1-phenyl-5-pyrazolidone-3-carboxylic acid, $\text{COCH}_2\text{CH}(\text{COOH})\text{NHC}_6\text{H}_5$.

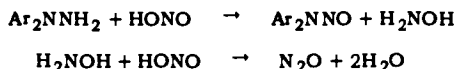
Phenylhydrazine reacts with lactones in the same manner as ammonia, forming hydroxy acid hydrazides.²³⁵

Phenylhydrazinesulfinic acid, $C_6H_5NHNHSO_2H$, is obtained by the action of sulfur dioxide on phenylhydrazine.²³⁶ The compound is converted on gentle heating to **thionylphenylhydrazone**, $C_6H_5NHN=SO$. The latter results also through the reaction of thionyl chloride, $SOCl_2$, with phenylhydrazine.²³⁷ **Phenylbenzenesulfazide**,



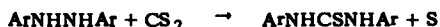
is obtained from phenylhydrazine and benzenesulfonyl chloride in ethereal solution; and from aqueous diazonium salts, by the action of sulfur dioxide or sodium hydrosulfite.²³⁸

Nascent *nitrous acid*, reacting with a well-cooled solution of a salt of a primary hydrazine, gives a very unstable nitroso derivative, $\text{ArN}(\text{NO})\text{NH}_2$, which on gentle heating with aqueous alkalis is converted to a *diazoimide*, ArN_3 . When the reaction of nitrous acid with hydrazines is carried out in the presence of excess acid, and at a higher temperature, the diazoimides are formed directly. Unsymmetrical diaryl hydrazines react with nitrous acid to form a nitrosoamine and nitrous oxide:



Phenylhydrazine reacting with carbon disulfide in ethereal solution gives phenyl-

hydrazine phenyldithiocarbazinate,²³⁹ $\text{C}_6\text{H}_5\text{NHNHCSSNH}_2\text{NHC}_6\text{H}_5$. When this compound is heated, it changes to diphenylthiocarbazide, $(\text{C}_6\text{H}_5\text{NHNH})_2\text{CS}$.²⁴⁰ The free phenyldithiocarbazinic acid is readily oxidized to the disulfide.²⁴¹ The reaction of hydrazo compounds with carbon disulfide results in the formation of thioureas:



Phenylhydrazine thiocyanate undergoes rearrangement to phenylthiosemicarbazide, $\text{C}_6\text{H}_5\text{NHCSNHNH}_2$, when heated at $160\text{--}170^\circ$.²⁴² When the latter is heated with concentrated sulfuric acid, it is converted to thiocarbazine, $\text{C}_6\text{H}_5\text{SCHNNH}$.

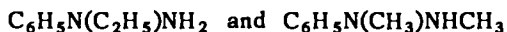
Phenylsemicarbazide, $\text{C}_6\text{H}_5\text{NHNHCONH}_2$, results through the reaction of salts of phenylhydrazine with potassium cyanate.²⁴³

Diphenylsemicarbazide, $\text{C}_6\text{H}_5\text{NHNHCONHC}_6\text{H}_5$, results through the reaction of phenylhydrazine with phenyl isocyanate. Similar compounds,



result through the reaction of hydrazobenzene, $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$, with phenyl isocyanate and phenyl isothiocyanate.²⁴⁴

Alkylated hydrazines which contain only one tertiary nitrogen, such as



combine with a molecule of alkyl iodide to form quaternary ammonium compounds, which are termed azonium compounds.²⁴⁵ More highly alkylated compounds are also formed in this reaction through the replacement of the hydrogen atom attached to the nitrogen atom with alkyl groups. Methyl iodide reacting with phenyltrimethylhydrazine, $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)\text{N}(\text{CH}_3)_2$, brings about a partial cleavage of this compound to an aliphatic and arylaliphatic amine. Other fully alkylated aromatic hydrazines also show this tendency toward cleavage on reaction with alkyl iodides.

Hydrazines are extremely susceptible to oxidizing agents, and act as strong reducing agents. Phenylhydrazine, even in very dilute condition, reduces Fehling's solution in the cold. Diazo compounds, $\text{ArN}=\text{NOH}$, are the first products formed when aromatic hydrazines are oxidized.²⁴⁶ Tetrazones are formed when α -alkyl aryl hydrazines are oxidized with mercuric oxide, provided the alkyl residue is saturated:



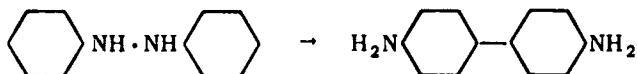
Allylphenylhydrazine may be converted to a tetrazone by oxidation with ferric chloride.²⁴⁷ More energetic oxidation of these compounds results in the formation of secondary amines:



When hydrazo compounds, ArNHNHAr , are reduced energetically they yield amines, ArNH_2 . Reduction takes place most readily at the time of formation of these compounds from azo compounds, and it is often difficult to prevent this reductive cleavage of hydrazo compounds during their preparation. Tetraaryl hydrazines can be reduced readily to secondary amines.

The Benzidine, Diphenylene, and Semidine Rearrangements

Hydrazobenzene, subjected to the action of strong mineral acids, undergoes molecular rearrangement giving benzidine:

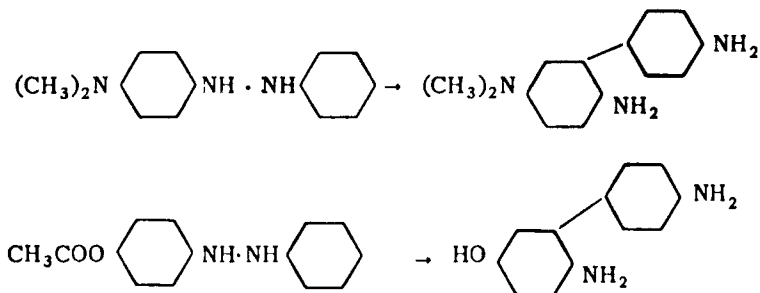


This transformation is of general occurrence and is known as the *benzidine rearrangement*.²⁴⁸ A small amount of 4,2-diaminodiphenyl is also formed by what is known as the *diphenylene transformation*. While the transformation is best effected with mineral acids, benzidine is also formed as its acylated derivative when hydrazobenzene is boiled with formic or acetic acid.

When azobenzene is reduced in acid solution, the hydrazobenzene first formed is converted to benzidine even when the reduction is carried out in the cold.²⁴⁹ The method is utilized for the commercial preparation of benzidines. The reduction is carried out with sulfurous acid in the presence of a little hydriodic acid. Conversion of hydrazo compounds to benzidines may be accomplished also by electrolytic reduction in 30% sulfuric acid containing 10% titanium sulfate, using lead electrodes, and a current density of 3 to 4 amps/cm² under 3 to 4 volts.

While many hydrazo compounds undergo the benzidine transformation in the cold, with some it is necessary to resort to heating in order to bring about the rearrangement. The application of heat causes secondary effects, however; it causes an oxidative-reductive process resulting in the formation of an azo compound and an amine from the hydrazo body.²²⁶ For that reason it is best to induce the transformation in such cases by means of stannous chloride and an alcoholic solution of hydrochloric acid in the cold.²⁵⁰ A portion of the hydrazo compound hereby undergoes cleavage by reduction, while another portion undergoes the rearrangement.

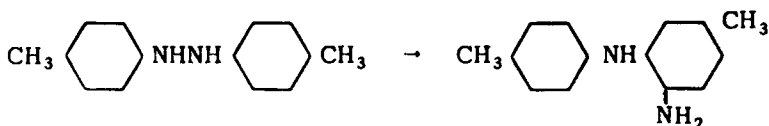
Hydrazobenzene derivatives in which chlorine or carboxyl groups occupy the *para* positions, undergo the benzidine transformation partially with removal of these substituents. The diphenylene transformation proceeds as the main reaction when a halogen atom or the groups (CH₃)₂N, CH₃COO are present in the *para* position in the hydrazo compound:



The diphenylene transformation is the principal reaction also when a methyl

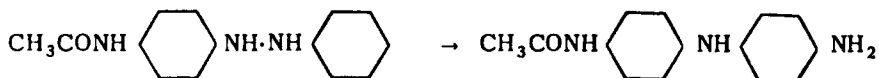
group is present in the *para* position in one ring, and an ethoxyl group in the *ortho* position in the other.

When *para*-hydrazotoluene is treated with aqueous mineral acids, it is in part transformed to *para*-azotoluene and *para*-toluidine, and in part to *o*-amino-4,3-ditolylamine. The latter compound is formed as the major product when *p*-hydrazotoluene is treated with stannous chloride and hydrochloric acid:



This transformation is known as the *Semidine rearrangement*.²⁵¹ The transformation is carried out in the cold in order to avoid cleavage of the N–N bond.

The free amino group in the transformation product may occupy the *ortho* or the *para* position, and consequently the transformation may be either of the *ortho* semidine or of the *para* semidine type. With doubly *para*-substituted hydrazo compounds, only the *ortho* semidine rearrangement occurs. Often the semidine and benzidine rearrangements take place side by side, so that semidine bases are obtained together with diphenyl bases. The semidine transformation takes place when the groups $\text{C}_2\text{H}_5\text{O}$ or CH_3CONH are present in the *para* position. *p*-Acetaminohydrazobenzene, for example, is converted to aceto-*p*-diaminodiphenylamine:

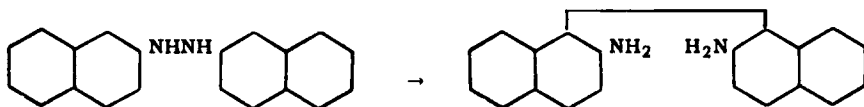


When both nuclei bear *para* substituents, then *ortho* semidine transformation takes place exclusively, unless at least one substituent is COOH , SO_3H , halogen, OCOCH_3 , or OAlk . The groups COOH and SO_3H are fully removed; halogens are removed occasionally, while OAlk groups are removed in some exceptional cases. The *ortho* semidine rearrangement becomes the principal reaction in the benzene series if one *para* position is occupied by a methyl or alkoxyl group. The transformation becomes the principal reaction in the α -benzenehydroxynaphthalene series if the *para* position in the naphthalene ring is occupied by an alkoxyl group. The transformation may be inhibited or completely prevented if the *ortho* position is also occupied. The wandering group in *ortho* semidine rearrangement always goes into the *ortho* position in the *para*-substituted ring.

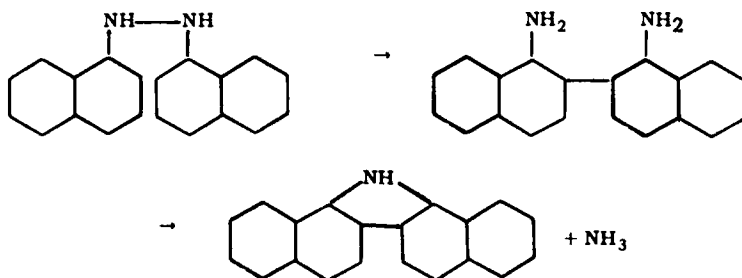
The *para* semidine transformation becomes the main reaction if one *para* position is occupied with an amino or acetamino group. The *para* semidine transformation takes place together with the *ortho* semidine transformation almost invariably if an alkoxyl group is present in one *para* position. The *para* semidine transformation accompanies the diphenylene transformation when chlorine, bromine, or a methyl group occupies the one *para* position. The *para* semidine transformation takes place with removal of an acetoxyl group if this group is present in *para* position in one ring.

Symmetrical substitution by the same group in the *para* position in both rings induces a tendency toward cleavage of the N—N bond. A hydroxyl or amino group in *ortho* or *para* position in one ring also induces this tendency.

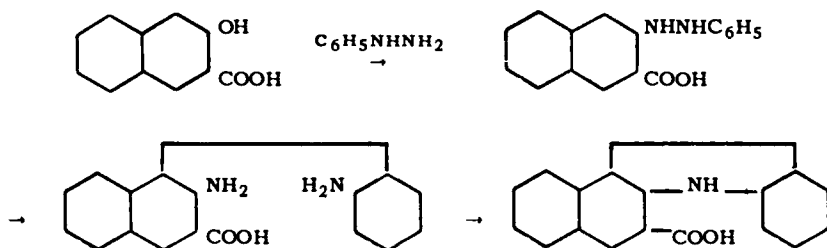
The hydrazo transformation in the naphthalene series often results in the formation of a *o,o'*-diamine:²⁵²



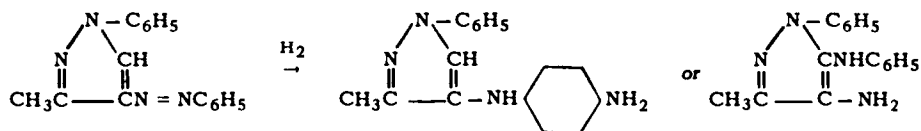
Ring formation may follow such *ortho* phenylene transformation, giving a carbazole. This occurs, for example, when α -hydrazonaphthalene is heated with concentrated hydrochloric acid giving dinaphthylcarbazole:²⁵³



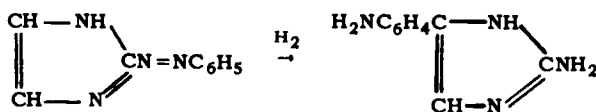
In the reaction of 2,3-hydroxynaphthoic acid with phenylhydrazine, the expected hydrazine apparently undergoes the *o,o'*-diphenylene rearrangement and the diamine undergoes ring closure to form a carbazole:²⁵⁴



The hydrazo group in some heterocyclic compounds is capable of undergoing the semidine transformation.²⁵⁵ 1-Phenyl-3-methyl-4-benzopyrazole, for example, is converted to an *ortho* or *para* semidine when reduced in acid solution:



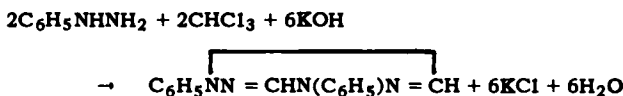
Glyoxylines behave in a similar manner when reduced in acid solution:²⁵⁶



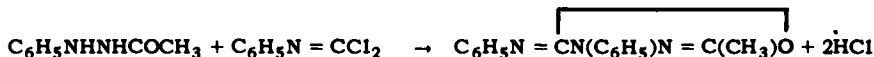
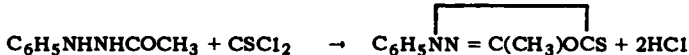
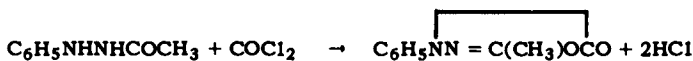
Formation of Cyclic Compounds from Hydrazines

Ring formation from aromatic hydrazines may involve the two nitrogen atoms present in a hydrazine, or it may involve one nitrogen atom in the hydrazine and a reactive group in ortho position in the aromatic nucleus, or one attached to the β -nitrogen in hydrazine. It may also involve two reactive groups in adjacent positions.

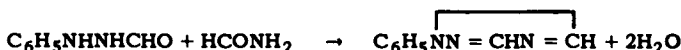
The reaction of chloroform with phenylhydrazine in the presence of potassium hydroxides gives rise to N-diphenylisodihydrotriazine:



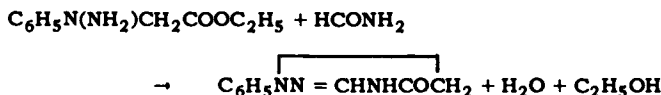
β -Acyl phenylhydrazides react with phosgene, thiophosgene, and isocyanophenyl dichloride to form isoxazoline derivatives:²⁵⁷



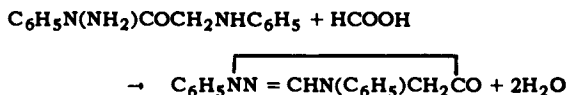
The reaction of formamide, with β -formylphenylhydrazine gives rise to N-phenyltriazole:²⁵⁸



Similarly, phenylhydrazino- α -acetic esters give phenylketotetrahydro- α -triazine with formamide:



and anilinoacetic- α -phenylhydrazide gives N-diphenylketotetrahydro- α -triazine with formic acid:



Phenylhydrazino- α -acetic esters reacting with potassium cyanate give 1-phenylsemicarbazide-1-acetic acid, and this on hydrolysis gives N-phenyldiketohexahydro- α -triazine.

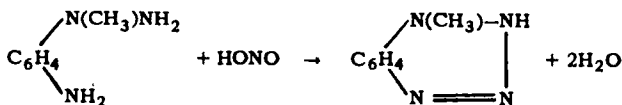
The reaction of diphenylcarbazide, $\text{C}_6\text{H}_5\text{NHNHCONHNHC}_6\text{H}_5$, with aromatic aldehydes in the presence of acetic acid and anhydrous sodium acetate leads to the formation of

1-phenyl-1,3-hydroxy-1,2,4-triazoles, $\text{C}_6\text{H}_5\text{NN} = \text{C}(\text{OH})\text{N} = \text{C} \cdot \text{Ar}$.²⁵⁹

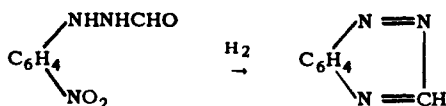
o-Nitrophenylhydrazine, boiled with caustic potash, gives azimido:



Phenomethyldihydrotetrazine results from the reaction of *o*-aminophenyl- α -methylhydrazine with nitrous acid:



α -Phenotriazine is formed on reducing β -formyl-*o*-nitrophenylhydrazine with sodium amalgam and acetic acid:



Azoxy, Azo, and Formazyl Compounds; Diazoimides

Azoxy Compounds²⁶⁰

The principal method of preparation of aromatic azoxy compounds, $\text{ArNO}=\text{NAr}$ is the *reduction of aromatic nitro compounds*:

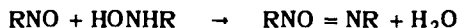


The oxygen in these compounds is attached to one nitrogen atom by a coordinate or semi-polar link.

Reduction of nitro compounds to azoxy compounds may be effected by use of a sodium alcoholate in alcoholic solution.²⁶¹ Reaction with sodium methoxide proceeds as follows:



At lower temperatures, the alcohol is oxidized to the corresponding aldehyde. Potassium alcoholates are often used for the purpose. Alkali metal ethoxides are more reactive than methoxides. It appears probable that a nitroso compound and hydroxylamine are formed as intermediates, and that the azoxy compound is formed as a result of their interaction:



Resin formation due to the aldehyde formed in the reaction may be prevented by the addition of hydrazine.

As an example, the preparation of azoxybenzol is carried out by dissolving 20 gm of metallic sodium in 200 gm of methanol, adding 30 gm of nitrobenzene and heating to boiling under reflux for five to six hours. On addition of water, an oil separates out which is allowed to solidify, is pressed free of any liquid, and is recrystallized from ligroin.

Azoxybenzene is obtained in excellent yield by heating nitrobenzene with a suspension of an excess of dry sodium methoxide in xylene.²⁶²

Some groups, such as methyl and hydroxyl, adversely affect the rate of reduction regardless of their position in the aromatic nucleus. Others, among them carboxyl, favorably affect the rate, carboxyl groups exerting their greatest effect when in the *ortho* position.²⁶³ The action of amino groups is interesting in that their effect increases as the acidity of the solution in which the reaction is carried out is increased.

Nitrodimethylanilines are converted successfully to azoxy compounds only by use of very concentrated sodium methylate solution.

A satisfactory procedure for the preparation of the azoxy compound from *m*-nitrodimethylaniline is to heat this compound with a methanolic solution of sodium methoxide at 100°, then to evaporate off the major portion of the alcohol at 125°, finally heating on the water bath for one hour without allowing the mass to become completely dry. Water is then added, the azoxy compound is allowed to solidify and is extracted with benzene or ligroin.²⁶⁴

Halonitro compounds may be successfully converted to haloazoxy compounds by reduction with sodium in absolute or 96% alcohol. Reduction should be carried out at 100-130°.²⁶⁵ In more dilute alcohol, *p*-nitrochlorobenzene is converted principally to *p*-nitrophenetole. With nitro compounds having a methyl group in the para position, partial removal of hydrogen from the methyl group takes place due to oxidation, with the formation of azoxy compounds of the dibenzyl or stilbene series.²⁶⁶ In the reduction of alkyl ethers of nitrophenols, an exchange of the alkyl group in the ether and that in the alcohol may occur.²⁶⁷

The reduction of nitro compounds to azoxy compounds may be effected in many cases by boiling with alcoholic caustic.²⁶⁸ The course of the reaction is identical with that taking place in the reduction with alkali metal alcoholates. Potassium hydroxide is more effective than sodium hydroxide, and the reducing action of ethyl alcohol surpasses that of methanol.²⁶⁹ Dinitro compounds are resinified when they are boiled with ethanolic sodium hydroxide, although methanolic sodium hydroxide converts *m*-dinitrobenzene to *m,m'*-dinitroazoxybenzene on 48 hours boiling.²⁷⁰ Reduction of dinitro compounds may be effected successfully by adding very concentrated aqueous sodium hydroxide to a solution of the dinitro compound in 96% alcohol. The reaction proceeds to completion within an hour, with the formation of a fairly pure dinitroazoxybenzene.²⁷¹ Nitroso compounds are also reduced to azoxy compounds by alcoholic caustic.²⁷²

The reduction of nitro compounds may be brought about also by use of aqueous solutions of alkaline arsenites:



In reducing nitrobenzene and *m*- and *p*-nitrobenzoic acids by this method, the calculated amount of arsenite is used, but with other nitro compounds, more arsenite may be required. Thus, for the reduction of *sym*-nitrosophthalic acid, about three times the calculated quantity of arsenite should be used.²⁷³

The reduction of nitro compounds to azoxy compounds proceeds well when an alkaline stannite is used as the reducing agent.²⁷⁴ The procedure is to dissolve stannous chloride in an excess of aqueous sodium hydroxide and to add the

resulting solution to one of the nitro compound in alcohol. Alternatively the nitro compound may be added to an aqueous solution of the stannite and the mixture heated under reflux while it is vigorously stirred. The unconverted nitro compound may be separated from the azo compound by steam distillation.

Zinc dust and *alcoholic caustic* may be employed for the reduction of nitro compounds to azoxy compounds. Some hydrazo compounds are also formed by this method of reduction.²⁷⁵

Other reducing agents employed for the purpose are *iron powder* and *caustic solution*,³⁰⁹ *ferrous sulfate* and *sodium hydroxide*,²⁷⁷ *iron pyrites* and *sodium hydroxide*,²⁷⁸ *dextrose* or *glucose* and *alkali*,²⁷⁹ *sodium sulfide* or *disulfide*,²⁸⁰ *sodium amalgam* and *alcohol*,²⁸¹ *magnesium amalgam*²⁸² and a mixture of *stannous oxide* and *sodium hydroxide*.

Azoxybenzene has been obtained through the electrolytic reduction of nitrobenzene by using a platinum anode and a nickel cathode in 2 to 4% aqueous alkali, with a current density of 5 to 7 amps/sq.decim.²⁷⁶ A quantitative yield of the azoxy compound has been obtained from m-nitrobenzophenone by reducing the compound electrolytically in alcoholic solution in the presence of sodium acetate.

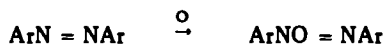
Cyclic azoxy compounds have been prepared by reducing dinitro dicyclic aromatic compounds having nitro groups in different rings.²⁸⁴

Azoxy compounds result through the reaction of a hydroxylamine with a nitroso compound:²⁸⁵



The reaction proceeds most readily in the presence of alkali.

Azoxy compounds may be prepared also by oxidizing azo compounds:²⁸⁶

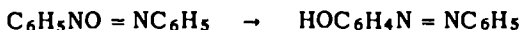


A 30% solution of hydrogen peroxide in glacial acetic acid is the best oxidizing agent for the purpose. Peracetic acid formed through the interaction of hydrogen peroxide and acetic acid, appears to be the essential reagent in this process. The reaction may proceed at room temperature, but it is sometimes necessary to heat the mixture on a water bath for several days. Yields are generally satisfactory, and often quantitative. Polyazoxy compounds have also been prepared by this method.²⁸⁷

Azoxy compounds are insoluble in water and are of neutral reaction. They cannot be distilled without decomposition. Nearly all crystallize well, and some behave as anisotropic liquids, i.e. as liquid crystals over a range of temperature immediately above their melting points. Many have been separated into optical isomers.²⁸⁸ They are not attacked by alkalies and dilute acids. They are resistant to oxidizing agents, unless a hydroxy or amino group is attached to one or both aromatic groups. When heated with iron filings they are reduced to

azo compounds.³²⁹ Selective reduction of structural isomers has been accomplished.³³⁰ Azoxy compounds add two bromine atoms to form loose adducts, such as $\text{C}_6\text{H}_5\text{N}(\text{O}) = \text{NC}_6\text{H}_5\text{Br}_2$.³³²

Azoxy compounds may be converted to hydroxy azo compounds by molecular rearrangement (*Wallach transformation*):²⁸⁹



The procedure is to heat the azoxy compound with concentrated sulfuric acid and to pour the product into water, whereupon the hydroxy azo compound separates as a colored solid, soluble in alkalis. The transformation may be brought about also with chlorosulfonic ester, which yields the chlorosulfonic ester of the hydroxyazo compound.³³¹

On heating azoxybenzene with sulfuric acid at 200° , *p*- and *o*-hydroxyazobenzenes are formed; on heating with acetic anhydride, only the *ortho* compound is formed.²⁹⁰

o-Aminoazobenzene heated with sulfuric acid yields phenylazimidobenzene:²⁸³



Azo Compounds

Azo compounds, $\text{ArN} = \text{NAr}$, may be obtained by heating azoxy compounds with iron filings. They may be formed directly from nitro compounds by treatment with zinc dust and alcoholic caustic.²⁹¹ A small amount of hydrazo compound is also formed, which may be oxidized to the azo compound with nitric acid, or by passing a current of air through the reaction mixture. On the technical scale, iron and aqueous caustic is used as the reducing agent. The reaction proceeds in an unsatisfactory manner with nitro compounds bearing substituents in the aromatic ring.

Conversion of nitro compounds to azo compounds takes place readily when the nitro compound is heated with the calculated amount of sodium stannite:



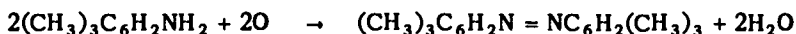
The stannite is dissolved in sodium hydroxide solution, an alcoholic solution of the nitro compound is added, and the mixture is heated on a water bath. The use of potassium stannite is preferable in reducing nitrosulfonic acids.²⁷⁴ The method is not suitable for the preparation of azonaphthalene.

Sodium amalgam and stannous oxide have also been employed for the reduction of nitro compounds to azo compounds.²⁷⁴ Reduction has also been effected with sodium arsenite,³³³ and lithium aluminum hydride.³³⁴ Alkali metal sulfides in strongly alkaline solution are employed on the technical scale for the preparation of azo compounds.

Nitro compounds may be converted to azo compounds by electrolytic reduction in alcoholic solution in the presence of some sodium hydroxide or sodium acetate, by use of mercury electrodes.³²⁵ Reduction can also be effected successfully

ly in alkaline plumbite solution with a lead cathode and a platinum or graphite anode. Reduction may be effected simply by electrolysis of a suspension of the nitro compound in caustic solution of 40 to 50° Bé heated at 105 to 115°, using a silver vessel as a cathode.

Azo compounds may also be formed through the oxidation of primary amines:²⁹²



Peracids, potassium permanganate, or potassium ferricyanide in alkaline solution and sodium hypochlorite are used as the oxidizing agent. This reaction proceeds well with amino compounds containing side chains.²⁹³

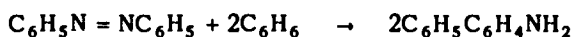
Oxidation of hydrazo compounds also gives azo compounds.³⁴⁴ The oxidizing agents used are, among others, nitrous oxides, mercuric oxide and potassium permanganate.

Azo compounds are formed through the condensation of primary aryl amines with aryl nitroso compounds in glacial acetic acid or in pyridine.³⁴⁵ The method makes possible the preparation of unsaturated mono and polyazo compounds which are often obtained in excellent yields.

Aromatic azo compounds result through the reaction of aromatic amino compounds with nitro compounds in the presence of powdered alkali at 180-200°.³³⁵ An azoxy compound is first formed and under the conditions of the reaction is reduced to an azo compound. This reaction makes possible the preparation of unsymmetrical as well as symmetrical compounds.

Azo compounds are formed by the reaction of diazo compounds with aromatic bodies by the so-called *coupling reaction*. This subject is treated in the following chapter.

Azobenzene reacts with benzene in the presence of aluminum chloride to form *p*-aminodiphenylamine:³¹¹



The reaction is of general applicability and permits the introduction of the grouping $\text{C}_6\text{H}_4\text{NH}_2$ into aromatic compounds. It should be carried out at the lowest possible temperature and the reagents must be quite pure.

Many azo compounds may be distilled without decomposition and are not changed on boiling with acids or alkalis. They are readily reduced to hydrazo compounds by alkaline reducing agents, such as zinc dust and sodium hydroxide solution, or ammonium sulfide.

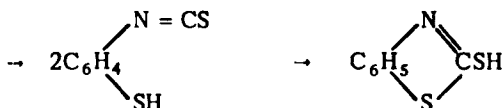
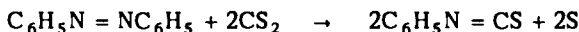
Azo compounds exist in *cis* and *trans* modifications. *Trans* azobenzene is converted to the *cis* isomer by irradiation. The latter may be removed by adsorption with alumina from its solution in benzene or light petroleum.³¹⁰

Aromatic azo compounds are very stable and can be brominated, nitrated, and sulfonated without undergoing breakdown or other fundamental change.

Reducing agents cause the breakdown of varying proportions of azo compounds into amines, depending on their strength and on the character of the azo compound. Hydriodic acid reduces azo compounds to amines with liberation of iodine.³³⁸

Azo compounds are converted to azoxy compounds by oxidizing agents. Oxidation with potassium permanganate or ceric sulfate forms the basis of a volumetric or colorimetric determination of the azo group.³³⁹

Azo compounds suffer rupture of the nitrogen-to-nitrogen linkage when treated with carbon disulfide at 260 to 270°. ²⁹⁴ The product formed is a mercaptobenzo-thiazole:

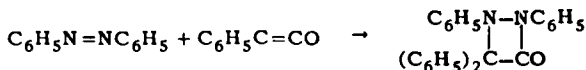


The azo group has weakly basic properties and forms loose salt-like compounds with halogen acids by reaction at moderate temperatures in non-hydroxylic solvents.³³⁶ The compounds have been formulated as ammonium salts or as quinoid bodies.³³⁷

Azo compounds combine additively with arylsulfonic acids giving N-arylsulfonylhydrazo bodies, such as $\text{C}_6\text{H}_5\text{N}(\text{SO}_2\text{Ar})\text{NHC}_6\text{H}_5$.³⁴⁶ Adducts are formed between sodium bisulfite and hydroxyazo compounds of the naphthalene series and some diaminoazo compounds in the benzene series, such as chrysoidine.³⁴⁷

A dilithium adduct of azobenzene is formed by reaction of the latter with methyl-lithium.³⁴⁸ The adduct reacts with azobenzene to form the crystalline monolithium derivative. $\text{C}_6\text{H}_5\text{N} = \text{N}(\text{Li})\text{C}_6\text{H}_5$.

cis-Azobenzene gives the expected adduct with a four-membered ring with diphenylketene:³⁴⁹

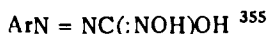


No adduct is formed with diazomethane.

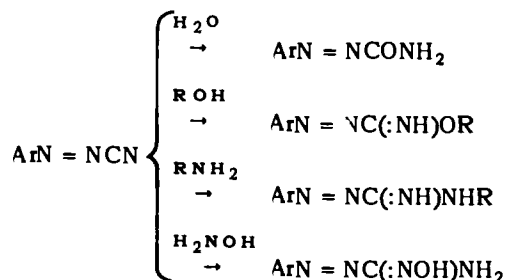
o-Aminazo compounds form benzotriazoles on oxidation, or by the action of thionyl chloride.³⁵⁰ 3-Keto-1,2,4-triazines are obtained with phosgene and with thiocyanates, with the latter on warming.³⁵¹ Anilinoiminazoles are formed by the reaction of *o*-amino-azo compounds and aldehydes.³⁵²

Arylazoformic Acids and their Derivatives

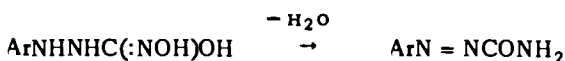
Derivatives of arylazoformic acids, $\text{ArN} = \text{NCOOH}$, are formed by oxidation of phenylsemicarbazides, phenylcarbazinates, and phenylhydrazoformhydroxamic acids, yielding arylazoformamides,³⁵³ esters,³⁵⁴ and hydroxamic acids,



They may be further formed through the hydrolysis, alcoholysis or aminolysis of aryldiazo cyanides³⁵⁶

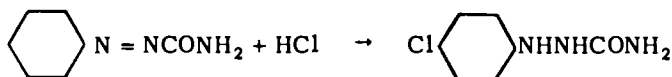


Finally, such derivatives are formed in good yield through the dehydration of arylazoformamides with acetic anhydride:³⁵⁵



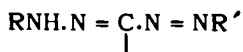
Azoformic acids with negative substituents are not known in the free state, but exist only in the form of their alkali metal salts. The potassium salts of such acids have been employed as the source of free aryl radicals in the preparation of organometallic compounds.³⁵⁸

The azoformic group, $-\text{N} = \text{NCO}-$, is highly reactive; with concentrated hydrochloric or hydrobromic acid, simultaneous reduction and nuclear halogenation proceeds, usually with good yields of the haloarylhydrazo derivative:³⁵⁹

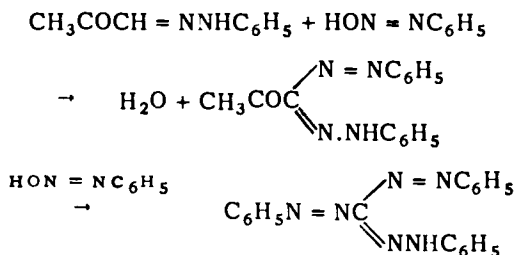


Formazyl Compounds²⁹⁵

Formazyl compounds, i.e., compounds containing the group

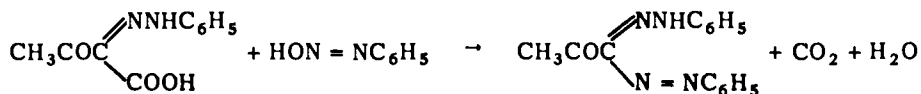


are formed readily through coupling reactions. They are formed, for example, when hydrazones with a primary hydrazoic residue are made to react with diazo compounds:



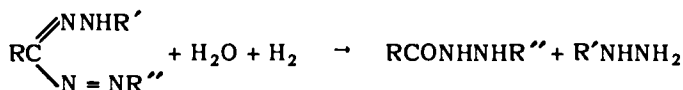
The reaction takes place also with hydrazones in which a removable group, such

as COOH or COCH_3 , is attached to the carbon atom joined to the nitrogen with a double bond:

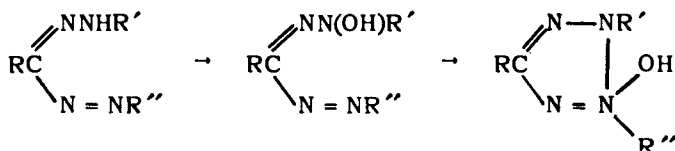


Since aliphatic compounds which contain a carbonyl, nitro, or other negative groups yield hydrazines with diazo compounds, they give formazyls directly when acted upon by a sufficient excess of diazobenzene. Acetone, for example, gives formazyl methyl ketone, $\text{C}_6\text{H}_5\text{N} = \text{NC}(\text{COCH}_3) = \text{N.NHC}_6\text{H}_5$, and acetoacetic ester gives formazylazobenzene, $(\text{C}_6\text{H}_5\text{N} = \text{N}_2) \text{C} = \text{N.NHC}_6\text{H}_5$.

Formazyl compounds are converted to a hydrazine and a hydrazide when reduced with zinc dust and aqueous sulfuric acid:

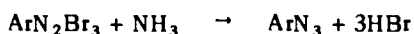


They are converted to tetrazonium hydroxides when oxidized:



Diazoimides

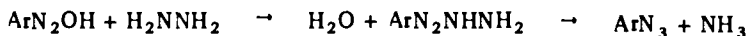
Diazoimides, or azides, RN_3 , are formed readily through the interaction of diazoperoxides and ammonia:²⁹⁶



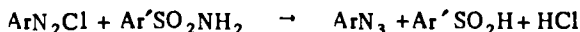
They are formed also by the action of nitrous acid on hydrazines,²⁹⁷



and through the reaction of diazo compounds with hydrazines:²⁹⁸



An aryl azide is the chief product of the reaction between an aromatic diazo compound and hydroxylamine, when a mixture of the solutions of the two compounds is made alkaline.²⁹⁹ Excellent yields of aryl azides are obtained when hydroxylamine is replaced by its O-alkyl or O-aryl ethers, or by its potassium mono- or disulfonate.³⁶⁰ Azides are also formed through the reaction of diazonium salts with chloramine;³⁶¹ or by the interaction of diazonium salts with sulfonamides:³⁶²



The reaction is of wide applicability and yields are generally high.

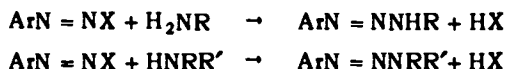
Aryl azides may be prepared also by oxidizing aryldiazoamides with potassium hypobromite or with ammoniacal silver nitrate.³⁶³ They may be obtained further through the reaction of hydrazoic acid with diazonium salts.³⁵⁷

Diazoimides are of neutral reaction. They explode when heated excessively. They offer a convenient source of the radicals ArN: in the presence of aluminum chloride.³²⁸

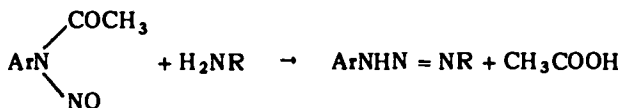
Aromatic Compounds with a Chain of Three or More Nitrogen Atoms

Only a limited number of compounds with chains of three or more nitrogen atoms are known, because the stability of compounds with a nitrogen chain of such length is slight and decreases with increase in the number of nitrogens in the chain.

Triazenes, $\text{RN} = \text{N} \cdot \text{NHR}'$ and $\text{RN} = \text{N} \cdot \text{NR}'\text{R}''$, also known as diazoamino compounds, are formed through the reaction of amines with diazo compounds:



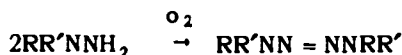
The reaction is considered in Chapter 27 dealing with diazo compounds. Triazenes are also formed by the reaction of nitrosoanilides with primary amines in alcoholic solution:³⁰⁰



Diazo-hydroxylamino compounds $\text{ArN}:\text{NN}(\text{OH})\text{Ar}'$ are tautomeric with triazene oxides, $\text{ArNHN}:\text{N}(\text{O})\text{Ar}'$.³²⁷

Diazoamino compounds are very weak bases. They form unstable double platinum chlorides. The hydrogen atom attached to nitrogen is replaceable with metals.³⁰¹ Sodium dissolves in an ethereal solution of diazoaminobenzene with evolution of hydrogen and the formation of the sodio compound which remains in solution. The silver salt results on mixing alcoholic solutions of diazoaminobenzene and silver nitrate. Diazoaminobenzene is decomposed to aniline and nitrogen when boiled with hydrochloric acid, although many other diazoamino compounds are very stable toward boiling acids.³⁰² Diazoamino compounds behave, on the whole, much like diazo compounds, although they are markedly less reactive than the more reactive among diazo compounds.

Symmetrical tetrazenes with the double bond in the middle of the nitrogen chain are formed by the oxidation of unsymmetrically disubstituted hydrazines:



The reaction is general for all *unsym*-disubstituted hydrazines. Best results are obtained with azo carbonic ester, $\text{C}_2\text{H}_5\text{OCON} = \text{NCOOC}_2\text{H}_5$, which is converted to the corresponding hydrazo ester.³⁰³ Mercuric oxide, ferric chloride, and hypochlorous acid have also been employed as oxidizing agents.

All *sym*-tetraaryltetrazenes lose nitrogen at 120-140° and are converted to tetrasubstituted hydrazines. They form unstable salts. Tetraphenyltetrazene is converted on reduction to diphenylamine.

Benzylene derivatives, $\text{ArN} = \text{NNHNHR}$, result through the reaction of hydrazines RNHNH_2 with diazo compounds.³⁰⁴

Hexaryltetrazanes, $\text{RR}'\text{NNR}''\text{NR}'''\text{NRR}'$, are prepared by the oxidation of tri-substituted hydrazines, $\text{RR}'\text{NNHR}''$, usually with lead peroxide or potassium ferricyanide in an inert solvent. These compounds are stable only at low temperatures. They dissociate into free radicals in solution.³⁰⁵ These radicals combine with other free radicals and nitric oxide.

Hexaphenyltetrazene, $(\text{C}_6\text{H}_5)_2\text{NN}(\text{C}_6\text{H}_5)\text{N}(\text{C}_6\text{H}_5)\text{N}(\text{C}_6\text{H}_5)_2$, is stable only in the neighborhood of -80, at which temperature it is a solid. The compound dissociates into free radicals in solution.

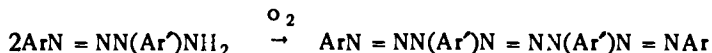
The free radical $(\text{C}_6\text{H}_5)_2\text{NNC}_6\text{H}_2(\text{NO}_2)_3$, resulting from the dissociation of tetraphenylbistrinitrotetrazane is remarkable in that it is quite stable and has been prepared in the form of deep violet crystals.

Hydrotetrazones, such as $\text{C}_6\text{H}_5\text{CH} = \text{NN}(\text{C}_6\text{H}_5)\text{N}(\text{C}_6\text{H}_5) \cdot \text{N} = \text{CHC}_6\text{H}_5$, result through the oxidation of simple aldehyde phenylhydrazones.

The only known pentazene derivatives are the bisdiazamino compounds $\text{ArN} = \text{N} \cdot \text{NR} \cdot \text{N} = \text{NAr}$. They are obtained readily by the reaction of aliphatic amines with aromatic diazo compounds.³⁰⁶ The reaction of aromatic diazo compounds with primary aromatic amines usually proceeds only to the diazoamino stage. Pentazene can be obtained sometimes when the reaction is carried out in alkaline solution.

Bis diazo compounds are less stable than the corresponding diazo compounds and explode more readily.

Octazenes, $\text{ArN} = \text{NN}(\text{Ar}')\text{N} = \text{NN}(\text{Ar})\text{N} = \text{NAr}$, more correctly termed octaztrienes, are formed when diazohydrazides resulting from the reaction of aromatic hydrazines with diazo compounds are oxidized in ethereal solution at 0° with dilute aqueous permanganate:³⁰⁷



These compounds are low melting, very unstable, explosive solids. They undergo decomposition rapidly and spontaneously even at low temperatures.

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 87. Lauth, *Ber.*, 6, 677 (1873); Hofmann, *ibid.*, 10, 600 (1877).
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 89. Jones and Kenner, *ibid.*, 1932, 711.
 90. Schlömann, *Ber.*, 26, 1023 (1893).
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 92. Hepp, *Ber.*, 10, 327 (1877). Cf. Pictet and Crépeux, *ibid.*, 21, 1106 (1888).
 93. Blaschhoff and Mintz, *ibid.*, 25, 2314 (1892).
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 97. Hager, *Organic Syntheses*, 8, 116.
 98. Goldberg and Nimerovsky, *Ber.*, 40, 2448 (1907); Wieland and Sakellarios, *ibid.*, 52, 898 (1919).
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104. Seelig, *Ber.*, **23**, 2971 (1890); Scholts, *ibid.*, **24**, 2402 (1891); Posner, *ibid.*, **26**, 1856 (1893); Kraft, *ibid.*, **23**, 2780 (1890); Wolff, *ibid.*, **25**, 3038 (1892); Lellmann and Mayer, *ibid.*, **25**, 3581 (1892); Fiacher, *ibid.*, **26**, 468 (1893); Lellmann and Haas, *ibid.*, **26**, 2583 (1893).
105. Strakosch, *Ber.*, **5**, 692 (1872).
106. Strassmann, *ibid.*, **21**, 576 (1888); Brömme, *ibid.*, **21**, 2700 (1888); Salkowski, *ibid.*, **22**, 2142 (1889); Landau, *ibid.*, **25**, 3011 (1892); Wolff, *ibid.*, **25**, 3031 (1892); Poanar, *ibid.*, **26**, 1856 (1893).
107. Bamberger and Lodter, *Ber.*, **20**, 1709 (1887); Kröber, *ibid.*, **23**, 1026 (1890); Zanetti, *ibid.*, **26** Ref. 196 (1893).
108. Hofmann, *Ber.*, **1**, 102 (1868); Bamberger and Lodter, *ibid.*, **21**, 51 (1888).
109. Goldschmidt, *Ber.*, **19**, 3232 (1886); Blachier, *ibid.*, **26**, 1892, 1896, 1899 (1893); Blachier and Napieralaki, *ibid.*, **26**, 1905 (1893); Kann and Tafel, *ibid.*, **27**, 2306 (1894); Tafel, *ibid.*, **19**, 1928 (1886); **22**, 1856 (1889); Michaelis and Jacobi, *ibid.*, **26**, 2160 (1893).
110. Fiacher, *Ann.*, **241**, 328 (1887); Zaunachirm, *ibid.*, **245**, 279 (1888); Uebel, *ibid.*, **245**, 289 (1888).
111. Hofmann, *Ber.*, **18**, 2738 (1885); Hoogewerf and van Dorp, *Rec. trav. chim.*, **5**, 252 (1886).
112. Cf. Vaubel, *J. prakt. Chem.*, (2) **48**, 75, 315 (1893).
113. Cf. Hantzsch and Graf, *Ber.*, **38**, 2159 (1905).
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115. Cf. Langer, *ibid.*, **15**, 1328 (1882).
116. Cf. Heinichen, *Ann.*, **253**, 274 (1889).
117. Langer, *Ber.*, **15**, 1061, 1328 (1882). Cf. Michael and Norton, *ibid.*, **11**, 107 (1878).
118. Nötting and Collin, *Ber.*, **17**, 261 (1884).
119. Hübner and Frericha, *Ann.*, **208**, 299 (1881).
120. Merz et al., *Ber.*, **10**, 761 (1877); Nötting and Collin, *ibid.*, **17**, 268 (1884); Groll, *ibid.*, **19**, 198 (1886); Noelting, *ibid.*, **19**, 545 (1886).
121. v. Romburgh, *Rec. trav. chim.*, **2**, 31, 108, 305 (1883); **6**, 253 (1887); **8**, 215, 248, 273 (1889); Mertens, *Ber.*, **19**, 2123 (1886).
122. Körner, *Jahresb.*, **1875**, 344; Noelting and Collin, *Ber.*, **17**, 261 (1884).
123. Witt and Utermann, *ibid.*, **39**, 3903 (1906).
124. Nietzki and Benckiser, *Ber.*, **18**, 294 (1885); Turner, *ibid.*, **25**, 985 (1892); Wülfing, *Germ. patent* 65,212; 66,060; *Ber.*, **26** Ref. 115, 262 (1893).
125. Hübner, *Ann.*, **208**, 292 (1881).
126. Bayer and Co., *German patent* 72,173; *Ber.*, **27** Ref. 222 (1894).
127. Meisenheimer and Patzig, *ibid.*, **39**, 2533 (1906).
128. Muspratt and Hofmann, *Ann.*, **57**, 215 (1845); Anachütz and Heuiler, *Ber.*, **19**, 2161 (1886).
129. Wagner, *ibid.*, **7**, 76 (1874).
130. Perkin, *J. Chem. Soc.*, **113**, 508 (1918); Green and Rowe, *ibid.*, **113**, 67 (1918).
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132. Friedländer, *Monatsh.*, **19**, 627 (1899).
133. Ehrlich and Sacha, *Ber.*, **32**, 2341 (1899).
134. Fiacher and Hepp, *ibid.*, **20**, 1252 (1887).
135. Hofmann and Buckton, *Ann.*, **100**, 164 (1856); Heinzelmann, *ibid.*, **188**, 170 (1877); **190**, 226 (1877); Limpricht and Drebea, *Ber.*, **9**, 551 (1876); Zander, *Ann.*, **198**, 1 (1879); Limpricht and Biel, *Ber.*, **18**, 2182 (1885).
136. Cf. Fiacher, *Ann.*, **206**, 137 (1881).
137. Cf. Fierz and Köchlin, *Helv. Chim. Acte*, **1**, 223 (1918).
138. Lellmann, *Ber.*, **17**, 2719 (1884).
139. Kleemann, *ibid.*, **19**, 336 (1886).
140. Meyer, *ibid.*, **15**, 1977 (1882); Menachutkin, *J. prakt. Chem.* (2) **26**, 208 (1882).
141. Pawlewski, *Ber.*, **35**, 110 (1902).
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143. Chattaway, *Proc. Roy. Soc. London*, **1902**, 173; **1903**, 124.
144. Staedel, *Ber.*, **19**, 1947 (1886).
145. Nietzki and Benckiser, *ibid.*, **17**, 707 (1884).
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148. Leo, *Ber.*, **10**, 2134 (1877); Wallach, *ibid.*, **11**, 1590 (1878); **13**, 527 (1880); Hofmann, *ibid.*, **10**, 1095 (1877); **11**, 338 (1878); Bernthsen, *Ann.*, **192**, 29 (1878); *Ber.*, **11**, 503 (1878); Wallach et al., *ibid.*, **12**, 1061 (1879); **16**, 144 (1883); Jacobson, *ibid.*, **19**, 1067 (1886); **20**, 1895 (1887); Jacobson and Ney, *ibid.*, **22**, 905 (1889); Müller, *ibid.*, **22**, 2408, 2410 (1889); Holleman, *Rec. trav. chim.*, **12**, 290 (1893).
149. Jacobson, *Ber.*, **19**, 1067 (1886); **20**, 1895 (1887); **22**, 905 (1889).
150. Wallach, *ibid.*, **15**, 208 (1882); Tobias, *ibid.*, **15**, 2449 (1882).

151. Dains, *ibid.*, **35**, 2505 (1902).
152. Bamberger, *ibid.*, **27**, 585 (1894). Cf. Romburgh, *ibid.*, **29**, 1015 (1896); Hoff, *Ann.*, **311**, 91 (1900).
153. Angell, *Atti ecced. Lincei*, **14**, (1) 127 (1861); Bamberger, *Ber.*, **53**, 2321 (1920).
154. Hoff, *Ann.*, **311**, 99 (1900).
155. Bamberger and Baudisch, *Ber.*, **42**, 3568 (1909).
156. Traube, *ibid.*, **24**, 360 (1891).
157. Paal and Kretschmer, *ibid.*, **27**, 1244 (1894).
158. Cleve, *ibid.*, **20**, 1534 (1887).
159. Michaelis, *Ann.*, **274**, 201 (1893); **310**, 137 (1900).
160. Cf. Michaelis and Schroeter, *Ber.*, **27**, 490 (1894); *Ann.*, **326**, 147 (1903).
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164. Rathke, *Ber.*, **11**, 958 (1878); Losanitch, *ibid.*, **24**, 3021 (1891). Cf. Hlasiwetz and Kachler, *Ann.*, **166**, 142 (1872).
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166. Lauth, *Bull. soc. chim.*, (2) **7**, 448 (1867); Hofmann, *Ann.*, **79**, 11 (1851); *Ber.*, **5**, 704 (1872); Claus and Rautenberg, *ibid.*, **14**, 620 (1881); Claus and Howitz, *ibid.*, **17**, 1324 (1884); Merrill, *J. prakt. Chem.*, (2) **17**, 286 (1878); Dafert, *Monetsh.*, **4**, 496 (1883); Gautier, *Ann.*, **240**, 69, 87 (1887).
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168. Vorländer and Spreckels, *ibid.*, **52**, 309 (1919).
169. Thomas, *J. Chem. Soc.*, **89**, 280 (1906).
170. Bamberger and Seligman, *Ber.*, **36**, 685 (1903); Witt and Kopetschni, *ibid.*, **45**, 1134 (1912).
171. Fischer and Trost, *ibid.*, **26**, 3083 (1893); D'Ana and Kneip, *ibid.*, **48**, 1144 (1915).
172. Green, *Ber.*, **26**, 2772 (1893).
173. Goldschmidt and Schmid, *ibid.*, **18**, 568 (1885); Nletski, *Ann.*, **215**, 158 (1882).
174. Nöiting and Baumann, *Ber.*, **18**, 1150 (1885). Cf. Heymanns and Königs, *ibid.*, **20**, 2395 (1887).
175. Fritzsche, *J. prakt. Chem.*, (1) **20**, 454 (1840); **28**, 202 (1843); Willstätter and Moora, *Ber.*, **40**, 2665 (1907); Willstätter and Dorogi, *ibid.*, **42**, 2147, 4118 (1909); Green and Woodhead, *J. Chem. Soc.*, **97**, 2388 (1910); **101**, 1117 (1912); Green and Wolff, *Ber.*, **44**, 2570 (1911).
176. Bandrowski, *Ber.*, **27**, 480 (1894); Willstätter and Meyer, *ibid.*, **37**, 1494 (1904).
177. Bamberger and Rudolf, *Ber.*, **39**, 4285 (1906); Jones and Hartshorn, *J. Am. Chem. Soc.*, **46**, 1840 (1924).
178. Hofmann, *Ber.*, **9**, 1299 (1876); Bedson, *ibid.*, **14**, 263 (1881).
179. Adkins and Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).
180. Hübner, *Ann.*, **208**, 278 (1881).
181. Ladenburg, *Ber.*, **9**, 219 (1876); **17**, 147 (1884).
182. Ladenburg, *ibid.*, **11**, 590, 600, 1648 (1873); Hinsberg, *ibid.*, **19**, 2025 (1886); **20**, 1585 (1887); Fischer and Wreszinski, *ibid.*, **25**, 2711 (1892); Hinsberg and Funcka, *ibid.*, **26**, 3092 (1893); **27**, 2187 (1894).
183. Bamberger, *Ber.*, **27**, 1347, 1549 (1894); Wohl, *ibid.*, **27**, 1434 (1894); Bamberger et al., *ibid.*, **28**, 248, 1222 (1895); **33**, 3626, 3642 (1900); **36**, 2700 (1903); **39**, 4259 *Ann.* **1** (1906); **42**, 2312 (1909); v. Pechmann and Nold, *ibid.*, **31**, 559 (1898).
184. Willstätter and Kubli, *Ber.*, **41**, 1936 (1908); Baudisch et al., *ibid.*, **49**, 191, 203 (1916); Goldschmidt, *Z. Electrochem.*, **9**, 725 (1903); *Z. physik. Chem.*, **71**, 437 (1910); Cohen et al., *J. Chem. Soc.*, **81**, 26 (1902); **87**, 1287 (1905). Cf. Lapworth and Pearson, *ibid.*, **119**, 765 (1921); Haworth and Lapworth, *ibid.*, **119**, 768 (1921).
185. Lapworth et al., *J. Chem. Soc.*, **119**, 765, 768 (1921).
186. Gattermann and Schmidt, *Ber.*, **29**, 2935 (1896).
187. Wislicenus, *ibid.*, **29**, 494 (1896).
188. Bamberger and Knecht, *ibid.*, **29**, 864 (1896).
189. Brand and Steiner, *ibid.*, **55**, 875 (1922).
190. Brand and Stohr, *Ber.*, **39**, 4058 (1906); **42**, 2478 (1909).
191. Gattermann, *ibid.*, **26**, 1845 (1893).
192. Cohen and Candisch, *J. Chem. Soc.*, **87**, 1257 (1905).
193. Cf. Behrend et al., *Ber.*, **22**, 384, 613 (1889); **23**, 1774 (1890); *Ann.*, **257**, 203 (1890); **263**, 175 (1891); **269**, 393 (1892); Beckmann and Koester, *ibid.*, **274**, 37 (1893); Lindner, *ibid.*, **275**, 133 (1893).
194. Ruggli and Bolliger, *Helv. Chim. Acte*, **4**, 635, 641 (1921); Heller and Böessneck, *Ber.*, **55**, 474 (1922).
195. Heller, *ibid.*, **39**, 2339 (1906); **41**, 2693 (1908).
196. Heller, *ibid.*, **44**, 2420 (1911).
197. Reissert, *ibid.*, **41**, 3925 (1908).

198. Heller, *ibid.*, **42**, 470 (1909). Cf. Heller *et al.*, *ibid.*, **42**, 4555 (1909); **47**, 2889 (1914).
199. Bamberger and Elger, *Ber.*, **36**, 1619 (1903).
200. Gabriel and Girard, *ibid.*, **54**, 1073 (1921).
201. Knecht and Thompson, *J. Soc. Dyers Colorists*, **36**, 215 (1920); Thompson, *ibid.*, **37**, 7 (1921); 491, Fischer, *Ann.*, **190**, 71 (1877); Strecker and Römer, *Ber.*, **4**, 784 (1871); Bayer, German patent 163,447; Pfannstiel and Janecke, *Ber.*, **75**, 1096 (1942). Cf. Reyckler, *Ber.*, **20**, 2463 (1887).
202. Fischer, *Ber.*, **8**, 589 (1875); *Ann.*, **190**, 67 (1878).
203. Bamberger and Kraus, *Ber.*, **29**, 1834 (1896).
204. Davies, *J. Chem. Soc.*, **121**, 715 (1922).
205. Meyer and Lecco, *Ber.*, **16**, 2976 (1883); Fischer, *ibid.*, **17**, 572 (1884); Bischler, *ibid.*, **22**, 2801 (1889); Bischler and Brodskel, *ibid.*, **22**, 2815 (1889); Möhlau, *ibid.*, **45**, 2233, 2244 (1912); Angeli and Jolles, *ibid.*, **62**, 2099 (1929).
206. Hantzsch, *Ber.*, **30**, 339 (1897).
207. Fischer, *ibid.*, **17**, 2844 (1884); Fischer and Ehrhard, *Ann.*, **199**, 325 (1879); Michaelis and Claessen, *Ber.*, **22**, 2233 (1889); Paal and Bodewig, *ibid.*, **25**, 2896 (1892).
208. Michaelis, *Ber.*, **19**, 2450 (1886); Phillips, *ibid.*, **20**, 2485 (1887);
209. Fischer, *Ber.*, **8**, 1642 (1875); *Ann.*, **190**, 150 (1877); **236**, 198 (1886).
210. Widman, *Ber.*, **26**, 946 (1893).
211. Phillips, *ibid.*, **20**, 2485 (1887).
212. Bamberger and Tichvinsky, *ibid.*, **35**, 4179 (1902).
213. Alexejew, *Zeitschrift für Chemie*, **1868**, 497.
214. Hofmann, *Jahresb.*, **1863**, 424; Mukerji, *J. Chem. Soc.*, **121**, 2879 (1922); Bamberger and Grob, *Ber.*, **35**, 72 (1902).
215. Wiallcenus, *J. prakt. Chem.*, (2) **54**, 18, 62 (1896).
216. v. Auwers and Eckardt, *Ann.*, **359**, 357 (1908); v. Auwers, *ibid.*, **365**, 291 (1909).
217. Walther, *J. prakt. Chem.*, (2) **52**, 141 (1895).
218. Diels and Rhodius, *Ber.*, **42**, 1072 (1909).
219. Clam and Heumann, *ibid.*, **13**, 1181 (1880); Limpricht, *ibid.*, **18**, 1404 (1885); Noetting and Stricker, *ibid.*, **21**, 3139, 3142, 3143 (1888); Alexejew, *Zeitschrift für Chemie*, **1868**, 497.
220. Haussermann and Cöthner, *Chem. Ztg.*, **17**, 129, 209 (1893).
221. Fischer, *Ann.*, **190**, 132 (1878); **253**, 2 (1889); Willgerodt *et al.*, *J. prakt. Chem.*, (2) **37**, 345 (1888); **40**, 252 (1889); **44**, 67 (1891); Robert, *Rec. trav. chim.*, **56**, 419, 909 (1937); Mangini and Colonna, *Gazz. chim. ital.*, **68**, 708 (1938); Allen, *Organic Syntheses*, II, 228 (1943); Byrkit and Michalekin, *Ind. Eng. Chem.*, **42**, 1867 (1950).
222. Busch and Hobein, *Ber.*, **40**, 2099 (1907); Wieland and Fressel, *ibid.*, **44**, 901 (1911); **48**, 1119 (1915).
223. Chattaway and Ingle, *J. Chem. Soc.*, **67**, 1090 (1895).
224. Wieland *et al.*, *Ber.*, **39**, 1493, 1500 (1906); **40**, 4271 (1907); **45**, 2602 (1912).
225. Michaelis, *ibid.*, **19**, 2448 (1886); **20**, 43 (1887).
226. Cf. Melmus, *ibid.*, **3**, 554 (1870); Lermontov, *ibid.*, **5**, 235 (1872); Calm and Heumann, *ibid.*, **13**, 1180 (1880); Schultz, *Ann.*, **207**, 315 (1881); Stern, *Ber.*, **17**, 380 (1884).
227. Wieland, *Ann.*, **381**, 212 (1911); Wieland and Lecher, *ibid.*, **392**, 156 (1912).
228. Jarosky, *Monatsh.*, **31**, 951 (1910).
229. Fischer *et al.*, *Ber.*, **22**, 2728, 3220 (1889); **23**, 378, 802, 2625, 3107, 3110 (1890); **25**, 1254 (1892); Smith, *Ann.*, **272**, 182 (1892).
230. Schmidt and Schultz, *Ann.*, **207**, 327 (1881); Stern, *Ber.*, **17**, 380 (1884).
231. Michaelis, *Ber.*, **25**, 1550 (1892).
232. Widman, *ibid.*, **26**, 945 (1893); **26 Ref.** 816 (1893); **27**, 2964 (1894).
233. Michaelis, *Ann.*, **252**, 266 (1889).
234. Short, *J. Chem. Soc.*, **119**, 1445 (1921).
235. Wiallcenus, *Ber.*, **20**, 401 (1887).
236. Michaelis and Ruhl, *ibid.*, **23**, 474 (1894).
237. Kliebsen, *ibid.*, **27**, 2549 (1894).
238. Grandmougin, *ibid.*, **40**, 422 (1907).
239. Fischer, *Ann.*, **190**, 114 (1877); Liebermann and Seyewetz, *Ber.*, **24**, 789 (1891); Busch, *ibid.*, **27**, 2507 (1894).
240. Fischer, *Ann.*, **190**, 118 (1877); Fischer and Besthorn, *ibid.*, **212**, 316 (1882); Heller, *ibid.*, **263**, 278 (1891).
241. Fischer, *Ann.*, **190**, 114 (1877).
242. Fischer and Besthorn, *ibid.*, **212**, 324 (1882); Skinner and Rühemann, *Ber.*, **20**, 3374 (1887); Freund and Goldsmith, *ibid.*, **21**, 2465 (1885); Pellizzari and Trivoli, *ibid.*, **25 c**, 467 (1892); Harries and Lowenstein, *ibid.*, **27**, 861 (1894).
243. Fischer, *Ann.*, **190**, 113 (1877); Skinner and Rühemann, *J. Chem. Soc.*, **53**, 551 (1888); Pinner, *Ber.*, **20**, 2358 (1887); **21**, 1224, 2329 (1888); Pellizzari and Tivoli, *ibid.*, **25 c**, 467 (1892); Widman, *ibid.*, **26**, 2613 *Ann.*, (1893).
244. Goldschmidt and Rosell, *Ber.*, **23**, 490 (1890); Markwald, *ibid.*, **25**, 3115 (1892).

245. Harries, *Ber.*, **27**, 696 (1894); Fischer, *Ann.*, **190**, 102 (1877).
246. Fischer, *Ann.*, **190**, 99 (1877).
247. Fischer, *ibid.*, **190**, 182 (1877); Michaelis and Claassen, *Ber.*, **22**, 2235 (1889); **26**, 2174 (1893).
248. Zinin, *J. prakt. Chem.*, (1) **36**, 93 (1845); *Ann.*, **137**, 376 (1866); Hofmann, *Jehreab.*, **1863**, 424; Flittig, *Ann.*, **124**, 280 (1862); Wergo, *ibid.*, **165**, 202 (1873); Schultz, *ibid.*, **174**, 226 (1874); **207**, 311 (1881); Stern, *Ber.*, **17**, 379 (1884); Bandrowaki, *ibid.*, **17**, 1181 (1884); Clève, *Bull. soc. chim.*, (2) **45**, 188 (1886); Sacha and Whittacker, *Ber.*, **35**, 1435 (1902); Chapman, *J. Chem. Soc.*, **1933**, 806; Ingold and Kidd, *ibid.*, **1933**, 984.
249. Zinin, *Ann.*, **85**, 328 (1853); Schultz, *Ber.*, **17**, 472 (1884).
250. Cf. Täubner, *ibid.*, **25**, 1022 (1892).
251. Witt et al., *Ber.*, **20**, 1183 (1887); **24**, 1511 (1891); **25**, 1013 (1892); **27**, 2351, 2358 (1894); Täuber and Sieder, *ibid.*, **23**, 3798 (1890); Fischer et al., *ibid.*, **23**, 3798 (1890); **25**, 2826 (1892); **26**, 187, 378 (1893); **27**, 2780, 2782 (1894); Jacobson et al., *ibid.*, **25**, 992 (1892); **26**, 681, 688, 699 (1893); **27**, 2700 (1894); *Ann.*, **369**, 1 (1909); **427**, 148 (1922); See in *particular Ann.*, **428**, 76 (1922); Kehrman and Meainger, *Ber.*, **24**, 1239, 1799 (1891).
252. Jacobson, *Ann.*, **427**, 148 (1922).
253. Nietzki and Goll, *Ber.*, **18**, 3252 (1885).
254. Schöpf, *ibid.*, **29**, 265 (1896).
255. Michaelis and Schaefer, *Ann.*, **407**, 231, 260, 270 (1915).
256. Pymann et al., *J. Chem. Soc.*, **115**, 222, 224, 238, 244, 250, 257 (1919); **117**, 1428 (1920).
257. Freund et al., *Ber.*, **21**, 2456 (1885); **23**, 2821 (1890); **26**, 2870 (1893).
258. Pellizzari, *Gez. chim. ital.*, **24** II, 222 (1894).
259. Odde, *ibid.*, **45** I, 238 (1915).
260. Bigelow, *Chem. Rev.*, **9**, 117 (1931).
261. Brühl, *Ber.*, **37**, 2076 (1904); Antener, *Helv. Chim. Acta*, **21**, 812 (1938).
262. Prud'homme, *Bull. soc. chim.*, (3) **7**, 621 (1892).
263. Goldschmidt et al., *Z. physik. Chem.*, **48**, 435 (1905); **56**, 1, 385 (1906); **71**, 437 (1910).
264. Nöling and Fourniaux, *Ber.*, **30**, 2932 (1897).
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CHAPTER 27

AROMATIC DIAZO COMPOUNDS

Methods of Formation¹

Primary aromatic amines reacting with nitrous acid give diazonium compounds:



The direct reaction between nitrous acid and the amine proceeds readily with comparatively strong amines. With amines that are soluble in aqueous acids, the solution of the amine in the aqueous acid is treated with sodium nitrite solution. This procedure is known as the *direct method*. With amines containing acidic groups, the procedure is generally reversed, the solution of the amine in aqueous caustic, mixed with the required amount of sodium nitrite, being added to the acid. This procedure is known as the *inverted method*. The diazo compounds are obtained in the form of their aqueous solutions by these methods. When it is desirable to prepare the solid diazo compound, a solution or suspension of the amine salt in an inert liquid is treated with amyl nitrite or nitrosyl chloride, whereupon the diazo compound separates as a solid. This procedure has been originated by *Knoevenagel*. Weakly basic amines which do not dissolve in dilute acids are diazotized by treating their solution in concentrated sulfuric acid with nitrous acid; the active agent in this case is nitrosylsulfuric acid. Such amines may also be diazotized by adding metabisulfite to a solution of the amine in nitric acid. This method, which was originated by Witt, is applicable only to amines unaffected by nitric acid. These various methods will be considered in detail.

The Direct Method²

In this method, an aqueous solution of sodium nitrite is added rapidly or all at once, to the cooled solution of the amine salt in water.

If the amine salt is not completely soluble in the cold, a very fine suspension of the salt is prepared by dissolving the amine in the warm aqueous acid and cooling the solution rapidly. In general $2\frac{1}{4}$ to $2\frac{1}{2}$ molecular equivalents of acid are employed. As the basicity of the amine decreases, the amount of acid used is increased sufficiently to cause the complete solution of the amine when warmed. If an amount of acid in excess of the minimum required for complete solution is used, the amine salt may be thrown out in lumps that resist the action of nitrous acid. If an organic acid is used, very large quantities are required for satisfactory results; thus, in diazotizing aniline, eleven equivalents of acetic acid are required.

The optimum temperature range for satisfactory diazotization is 0° to 2° for simple

bases; 0° to 5° for meta halogenated amines, and 10° to 12° for benzidine bases, naphthylamines, and ortho and para halogenated bases. In some cases it may be necessary to carry out the reaction at ordinary, or even at somewhat elevated temperature. The safe working temperatures for a number of substituted amines are, *p*-nitroaniline 34° , *m*-nitroaniline 37° , *p*-chloroaniline 37° , *o*-anisidine 40° , *o*-chloroaniline 42° , *o*-nitroaniline 58° .³

Temperatures below that of room are maintained by the addition of ice to the reaction mixture; cooling is continued for 10 to 15 minutes after the introduction of all the nitrite. Delay in the addition of the nitrite may result in the formation of diazo amino compounds; the formation of these compounds may be avoided by adding the nitrite solution all at once.

The end point of the reaction is determined by means of starch iodide paper, which rapidly assumes a deep blue color in the presence of free nitrous acid. Another method consists in neutralizing the solution, whereupon a precipitate forms or a yellow coloration develops if an excess of amine is present.

It is important to use as nearly as possible the exact equivalent of the nitrite and the amine. The theoretically calculated amount of acid is seldom sufficient. In the diazotization of aniline and its homologs it is usual to employ an excess of one half the equivalent of the acid. In many other cases a larger proportion of the acid is required. It should be noted that concentrated hydrochloric acid reacts with sodium nitrite to form chlorine, which causes side reactions; for this reason the concentration of hydrogen chloride in the reaction mixture should not be allowed to exceed 20%.

At the completion of the reaction, any excess of nitrous acid is destroyed by adding urea, or preferably sulfamic acid, H_2NSOOH .

The method is applicable to amines of comparatively high strength that readily dissolve in aqueous mineral acids, including aniline and its homologs, aminophenol ethers, monohaloanilines, benzidines and α - and β -naphthylamines. Sulfonated amines that are soluble in aqueous acids may also be diazotized by this method.

The diazotization of 1,2- and 2,1-aminonaphthols or their sulfonic acid and other derivatives can only be carried out satisfactorily by using just sufficient acid to form the amine salt and adding one equivalent of zinc salt or a small amount of a copper salt to the reaction mixture. If a copper salt is employed, the copper must be carefully removed after the completion of the reaction.

With amines of equal basicity, the velocity of diazotization is greatest for an amine with an ortho substituent, least for one with a meta substituent. Substituents that influence the basicity of the amine show two opposite effects. Negative substituents cause an increase in the velocity of reaction, but simultaneously decrease the concentration of the reactive unit, the amine salt, by a reduction of basicity. Of the three amino compounds $p\text{-H}_2\text{NC}_6\text{H}_4\text{N}(\text{CH}_3)_3\text{Cl}$, $p\text{-H}_2\text{NC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_3\text{Cl}$ and $p\text{-H}_2\text{NC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{Cl}$, the last is diazotized most rapidly when one equivalent of acid is used, although all are diazotized at the same rate when an excess of acid is used. Negative substituents increase the velocity of diazotization in the order $\text{Cl} < \text{COOH} < \text{SO}_3\text{H} < \text{NO}_2$.

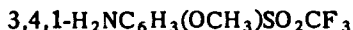
The velocity of diazotization increases as the concentration of hydrogen chloride is increased from 0.05*N* to 4*N*. The rate of diazotization is fourfold greater when hydrobromic acid is used instead of hydrochloric acid. The velocity of diazotization is lower when nitric, sulfuric and naphthalene sulfonic acids are employed instead of hydrochloric acid.⁴

Bases such as *p*-nitroaniline and 2,5-dichloroaniline have been diazotized successfully by this method by grinding the amine with concentrated hydrochloric acid in a stone edge runner mill and adding solid sodium nitrite in portions to the slurry. Many of these amines react in satisfactory manner when they are ground to pass a 40-mesh sieve; some must be ground to a greater degree of fineness. Fine subdivision may be brought about also by dissolving the amine in a fivefold excess of normal hydrochloric acid at 90°, then rapidly cooling the solution with ice.

Anilino-leucoindigotin⁵ and coordinated chromium compounds of the type $\text{HOCr}[\text{OC}_6\text{H}_3(\text{COOH})\text{NH}_2]_2$ and $\text{HO}[\text{CrB}_2][\text{OC}_6\text{H}_3(\text{COOH})\text{NH}_2]$, in which B is a non-diazotizable base,⁶ can be diazotized successfully. Amino aryl lead compounds of the type $(\text{C}_6\text{H}_5)_3\text{PbC}_6\text{H}_4\text{NH}_2$ can also be diazotized.⁷

Certain diazo compounds are so stable as to permit their preparation at a higher temperature; 2-aminobenzofuran is among such compounds.

3-Amino-4-methoxyphenyl-1-trifluoromethylsulfone,



is diazotized in acetone solution in the presence of zinc chloride and acid.⁸

Acylation of the amino group usually prevents diazotization, but sulfamic acids, ArNHSO_3H , nitramic acids, ArNHNO_2 , phosphamic acids are diazotized by cleavage of the inorganic acid groups.⁹

*The Inverted Method*¹⁰

In this method, a solution of the amino compound in alkali containing the required amount of the sodium nitrite is added to an excess of aqueous acid. Diazotization takes place immediately, and the diazo compound generally separates out as a solid.

Sulfamic acid, aminobenzoic acids, anilinedisulfonic acids, naphthylamine-sulfonic acids such as naphthionic acid, can be successfully diazotized by this procedure. The method is also applicable to weakly basic amines, such as nitroanilines, *o*-nitro-*p*-phenetidine, *o*-nitro-*p*-toluidine, aminoazobenzene and aminoazotoluene.

*Diazotization in Concentrated Acid (Claus Method)*¹¹

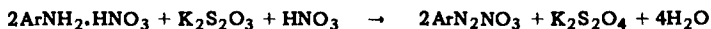
Weakly basic acids which are insoluble in dilute acids but soluble in concentrated acids may be diazotized in the latter. Concentrated sulfuric acid is usually employed for the purpose. Nitrosylsulfuric acid is generated in the solution by gradually adding powdered sodium nitrite, or a concentrated aqueous solution of this compound. Alternatively, the nitrite may be mixed with a portion of the sulfuric acid and the mixture added to the solution of the amine in sulfuric acid. The final mixture must be kept well agitated until a drop added to water fails to produce flocks of the free base, which indicates completion of the reaction. The mixture is then poured on ice.

p-Aminobenzaldehyde cannot be diazotized in solution in concentrated sulfuric acid, but may be diazotized in solution in sulfuric acid mixed with a large proportion of phosphoric acid.¹² Many other amines which resist diazotization by other methods have been diazotized successfully by this procedure. Diazotization of such amines can also be successfully carried out in solution in glacial

acetic acid by treatment with nitrosylsulfuric acid mixed with a moderate excess of sulfuric acid.¹³ Amines which are slowly diazotized with nitrosylsulfonic acid in concentrated sulfuric acid may sometimes be diazotized more rapidly in sulfuric acid containing a little water. Diazotization with nitrosyl sulfuric acid has been carried out successfully in pyridine, quinoline or isoquinoline solution.

*Witt's Method*¹⁴

Another method generally employed for the diazotization of negatively substituted aromatic amines is to dissolve the amine in concentrated nitric acid and to add potassium metabisulfite to the solution. The latter reduces a portion of the nitric acid to nitrous acid, and this reacts with the amine to form the diazo compound. The overall reaction may be expressed as follows:



This method can only be used for the diazotization of amines unaffected by concentrated nitric acid.

*Knoevenagel's Method*¹⁵

Amines may be diazotized by heating their salts with an alcoholic solution of amyl nitrite, the latter serving as the source of nitrous acid. The diazonium compound may be precipitated by adding ether to the reaction mixture. Glacial acetic acid and dioxane may also serve as the reaction medium. This method permits the preparation of diazonium salts in the dry state. In preparing halogenated benzenediazonium chlorides, such as *p*-chlorobenzenediazonium chloride, the use of an excess of acid must be avoided in order to prevent the formation of a sticky double compound with the acid. This method also serves for the diazotization of many weakly basic amines. For this purpose, the amine is dissolved in concentrated acid, the solution is diluted with water and cooled, and the nitrite is introduced dropwise.

Amino cinnamic acids have been successfully diazotized. The diazo compounds formed are capable of undergoing the various replacement reactions, and have been employed for the preparation of halogenated cinnamic acids.¹⁶

The diazotization of primary aromatic amines containing a secondary amino group is carried out by special techniques. A satisfactory procedure involves the use of two molecular proportions of nitrite, thus diazotizing the primary amino group and simultaneously nitrosating the secondary amino group. The resulting nitrosodiazo compound has satisfactory coupling properties. The nitroso group may be removed after the coupling reaction by heating with an acid or alkali, or by treatment with a reducing agent such as bisulfite.

Azoaminosulfonic acids are generally subjected to diazotization in the form of their crystalline sodium or ammonium salts obtained by cooling their hot, saturated aqueous solutions. These are treated with acid, then with sodium nitrite. Two and one half molecular proportions of acid are employed with compounds in which the sulfonic and amino groups are attached to the same radical; otherwise, three and one half molal proportions of the acid are added.

Tetrazotization of some diamines is possible, by working with small quantities, cooling thoroughly and rapidly mixing the solutions.¹⁷ When metaphenylenediamine has a substituent, tetrazotization is facilitated to such an extent

that it may be brought about by the direct method. Tetrazotization may be effected in glacial acetic acid with nitrosylsulfuric acid.¹⁸ The presence of a negative substituent often prevents the diazotization of one of the amino groups in a diamine; the second amino group can usually be diazotized after coupling the first diazo group. Acetylation of the amino group capable of undergoing diazotization may permit the diazotization of the obstructed amino group. A maximum of three diazo groups can apparently be attached to one benzene nucleus.¹⁹ *m*-Phenylenediamines do not, as a rule, yield diazo compounds when subjected to the usual conditions of diazotization. Diazo compounds are obtained, however, from 2,4-diamines having a substituent ortho to both amino groups. Tetrazotization of *m*-phenylenediamines is possible by the action of excess nitrous acid in concentrated hydrochloric acid,²⁰ although certain meta diamines fail to yield diazo compounds under these conditions.²¹

Only one amino group can be diazotized in 2,5-diaminobenzoic acid and 2-nitro-*p*-phenylenediamine.²² The amino group at position 4 can alone be diazotized in 2-nitro-*p*-phenylenediamine, 2,6-dichloro-*p*-phenylenediamine, *p*-phenylenediamine-2-sulfonic acid and 1,4-diaminonaphthalene-2-sulfonic acid. The amino group at position 1 in these compounds can be diazotized when that at position 4 is diazotized and coupled.²³ The amino group at position 1 in phenylenediamino-2-arsonic acid is diazotized.²⁴

Tetrazotization proceeds readily in the naphthalene series if two amino groups are attached to different rings,²⁵ but it proceeds with difficulty when both amino groups are attached to the same ring.²⁶

In the anthraquinone series, tetrazotization generally proceeds with ease. 1,5-Diaminoanthraquinone may be tetrazotized by nitrosylsulfuric acid, and the 1,4-diamino compound by Knoevenagel's method.²⁷ The amino group at position 1 cannot be diazotized in 1,4-diaminoanthraquinone-2,6- or -2,7-disulfonic acid, and in 2-chloro or bromo-1,4-diaminoanthraquinone. When halogen atoms are present at both 2 and 3 positions, one of the amino groups can be diazotized.

Some amino heterocyclic compounds are capable of forming diazo compounds. Diazo compounds may be obtained from 4-aminotriazole and its homologs,²⁸ 4-aminothiazole,²⁹ aminoantipyrine,³⁰ 5-amino-3,5-dimethylisoxazole,³¹ 3-aminoquinoline,³² aminotetronic acid,³³ and 3-aminopyridine.³⁴ 4-Aminopyridine and 5-aminoacridine can be diazotized by Witt's method, and 5-aminouracil-4-carboxylic acid by the inverted method. Unstable diazonium salts are obtained from triazoles and thiazoles.³⁵

An exchange of a negative group for a hydroxyl group may occur during the diazotization of amines containing strongly negative groups in *ortho* position with respect to the amino group. Exchange occurs most readily when the diazotization is carried out in the presence of weak acids. When dinitroanisidines are diazotized in glacial acetic acid, either a nitro group or a methoxy group may be exchanged, according to the orientation of the substituents.³⁶ It was observed, in connection with polynitroanisidines, that a group only became sufficiently mobile to be exchanged if it was *ortho* or *para* to the diazo group, and was at the

same time situated in *ortho* position with respect to a nitro position.³⁷ If conditions are such that either a nitro or a methoxyl group can be exchanged, the nitro group is exchanged preferentially.³⁸ If both the *ortho* and *para* positions in anisidine are occupied by negative groups, then almost invariably the *ortho* group will be found to be labile in some degree, and sometimes so reactive that it is exchanged in acid solution.³⁹ Nitroanisidines in which a nitro group is exchangeable are selfdiazotizing, once the diazotization reaction has been initiated.⁴⁰

Failure of the diazotization reaction may be due to oxidation of the amine by nitrous acid, and formation of nitroso compounds.⁴¹ The diazotization of readily oxidizable amines proceeds well in neutral or slightly acid media, especially in the presence of alkali and alkalineearth metal salts or salts of copper, zinc, and other metals. Amines diazotized by the direct method may yield a nitroso compound when treated with nitrosylsulfuric acid.

Miscellaneous Methods of Formation of Diazo Compounds

The reaction of nitrous fumes generated by heating a mixture of nitric acid with arsenious oxide with an amine salt gives a diazonium salt.⁴² This method, which was originated by Griess and was the first employed for the preparation of diazo compounds, is only of historic interest.

A number of other reactions result in the formation of diazo compounds. The reduction of the nitrate of an amine with zinc dust and hydrochloric acid; the reaction of nitroso compounds with hydroxylamine, and of nitric oxide with nitroso compounds⁴³ all lead to the formation of diazo compounds. The hydrolysis of nitrosoacetanilide, the reaction of sodamide with nitrobenzene,⁴⁴ the reaction of benzenesulfohydroxamic acid with phenylhydrazine and caustic⁴⁵ also give diazo compounds. Salts of phenylhydrazine, treated with mercuric oxide, or phenylhydrazines in alcoholic solution, treated with chlorine or bromine at a low temperature, yield diazo compounds.

Properties and Reactions of Diazo Compounds

Aromatic diazonium salts are, in general, very unstable.⁴⁶ Many decompose in aqueous solution if the temperature rises above 5°. Since decomposition is accelerated by light, their solutions must be protected from light. The solutions should not be kept for an unduly long period before use. The dry salts usually explode with violence when heated or struck. Benzenediazonium perchloride explodes when it is rubbed.⁴⁷ Even relatively stable diazo compounds may explode in the dry state; *o*-hydroxydiazo compounds of the naphthalene series form an exception. Stable salts may be obtained by precipitation with salts of alkaline earth and related metals. An excess of nitrous acid decreases the stability of the diazo compound. Ferrous ions also cause decomposition, although the presence of an excess of nitrous acid counterbalances their effect. Colloidal metals cause the rapid decomposition of diazo compounds in solution; copper is especially effective in this respect.⁴⁸

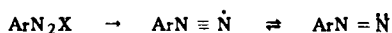
Changes in pH exert slight effect on the stability of certain diazo compounds, and a marked effect on that of others. Diazobenzene undergoes decomposition at a maximum rate at pH 12.7.⁴⁹ The stability of naphthalene- α -diazonium chloride decreases rapidly with increase in alkalinity.⁵⁰

In general, the more basic an amine, the more unstable is the diazo compound derived from it. Conversely, negative substituents, such as halogens, alkoxyl, nitro and sulfo groups increase the stability of the diazo compound. 2,4,6-Trichlorobenzenediazonium chloride and 2,4,6-tribromobenzenediazonium sulfate are stable in boiling water.⁵¹ *p*-Phenylenediamine, 2,6-dichloro- and monoacylated 2,5-disubstituted *p*-phenylenediamines give stable diazonium salts. Diazo compounds derived from aminobenzene and some of its derivatives also yield stable diazonium salts. An ether group in *ortho* position with respect to the amino group enhances the stability of the diazo compound.⁵² Stable diazo compounds are also obtained from *o*- and *m*-aminoazotoluenes, and azo compounds obtained from 1,7-aminonaphthols,⁵³ by coupling with various diazo compounds. Diazo derivatives of *o*-amino carboxylic acids can be salted out of solution and dried in vacuum at 40-50°. Diazonium salts derived from aminoanthraquinones are also sufficiently stable to be successfully crystallized from boiling water. *o*-Hydroxy azo compounds exhibit extraordinary light stability, at least in the absence of alkali. Positive substituents lower the stability of diazo compounds.

Diazoamino compounds may be decomposed without explosion by heating with sand or in solution in a high boiling solvent, such as aniline and paraffin.⁵⁴

Diazo compounds form salts with all strong inorganic acids as well as with a number of organic acids, especially sulfonic acids. Salts of diazonium compounds with strong mineral acids, such as the chloride or the nitrate, show a neutral reaction in aqueous solution, and give the ordinary ionic tests for the anion. The free diazonium hydroxides are strongly basic,⁵⁵ and can be accurately titrated by using Methyl Orange as indicator. The free bases are not sufficiently stable to be isolated in the pure form. The nature of the acidic group combined with the diazo compound has little effect on the stability of the diazonium salts.

Remarkable differences are observed in the chemical characteristics of diazonium compounds in acid, neutral and alkaline solution. The behavior of the diazonium ion in a strongly acid medium differs from that in neutral medium, because of an electromeric change in neutral medium which produces diazo ions. The extent of the change depends on the substituents in the aromatic nucleus, negative substituents favoring the rearrangement of the diazo form.⁵⁶ When caustic is added to the solution of the neutral diazonium salt, diazonium hydroxide is produced and immediately undergoes partial rearrangement to the normal diazo hydroxide:

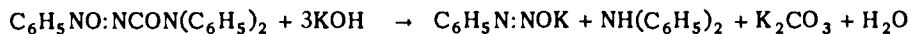


Reaction of caustic with normal diazo hydroxide gives rise to the normal diazotate. When an exact equivalent of alkali is added to the solution of the diazo hydroxide, the normal diazotate, both associated and dissociated, together with the free diazonium hydroxide are present in equilibrium. As more alkali is added, the proportion of normal undissociat-

ed diazotate increases. The normal diazotate, ArN:NOM , is converted on heating to isodiazotate ArNM.NO .⁵⁷

Metallic Diazotates and Isodiazotates

It was pointed out above that as caustic is added to the solution of a neutral diazonium salt, the free diazonium hydroxide first liberated is converted to the normal diazotate, ArN:NOM . It is possible to isolate the potassium benzenediazotate by salting out with an excess of caustic.⁵⁸ Diazotates are also obtained through the reaction of alcoholic caustic with arylazocarboxylic acids and arylazoxycarboxyamides and -anilides:⁵⁹



The ease with which this reaction proceeds depends on the character of substituents present in the aromatic nucleus and the amide group.

Diazotates cannot be obtained from diazo compounds in which a hydroxyl group is present in the *ortho* position with respect to the diazo group. Elements or groups at these positions which are replaceable by hydroxyl under the action of caustic, also exert the same effect as the hydroxyl group. A methyl group in *ortho* position to the diazo group may lead to ring closure, thus preventing the formation of diazotate. Diazonium salts with an aryl amino or alkyl amino group in the *para* position are converted to explosive compounds probably with a quinoid structure, $\text{ArN}=\text{C}_6\text{H}_4=\text{N}_2$. These compounds cannot be reconverted to the

original diazonium compound by treatment with acid.⁶⁰

The effect of substituents on the stability of diazotates is the reverse of that observed for diazonium salts, alkoxy groups in *ortho* and *para* position causing a decrease in stability.⁶¹

The conversion of normal diazotates to *isodiazotates* takes place with varying ease, depending on the nature of the diazo compound.⁶² When negative groups are present in the *ortho* or *para* position in the aromatic nucleus, the isodiazotate is formed on treatment with cold dilute caustic. *p*-Nitrodiazobenzene is converted to isodiazotate almost instantaneously when treated with dilute caustic at -10° , while diazobenzenesulfonic acid requires treatment with 4% caustic for 4 to 5 minutes. Diazobenzene can be converted to the isodiazotate only by warming to $130\text{--}135^\circ$ for a short period with concentrated potassium hydroxide.⁶³ Drastic treatment may also be necessary if the aromatic nucleus carries alkoxy groups. Good results are obtained only by rapidly heating to the conversion temperature. An excess of mineral acids converts normal and isodiazotates to diazonium salts. Treatment of an isodiazotate with acetic acid results in the formation of the free isodiazoo compound, which is acidic in character, and is soluble in ether, benzene and chloroform.⁶⁴

Normal diazotates are distinguished from isodiazotates by the fact that the former couple readily with aromatic amines or phenols and β -naphthol, while the latter couple with difficulty or not at all.⁶⁵ Nitramines, ArNM.NO_2 , are formed on oxidation of alkaline diazotates.

Diazo Anhydrides and Ethers

When metallic diazotates are treated with an equivalent of acid, they are converted to *diazo anhydrides*, $(\text{ArN}_2)_2\text{O}$, sometimes also improperly referred to as diazo oxides. These are highly colored, oils or explosive solids, which are converted by alkalis to diazotates, and to diazonium salts by acids. They react with metallic cyanides and sulfites to form the normal diazocyanides and diazosulfonates.⁶⁶ They react vigorously with benzene to form diaryls:



When silver diazotate is treated with an alkyl iodide, the O-alkyl ether of the diazo compound, ArN:NOAlk , is formed, whereas the reaction of an alkyl iodide with the sodium salt affords the N-alkyl ether, ArN(Alk)NO .⁶⁷ Nitrosoacyl derivatives, ArN(COR)NO , are formed on treatment of the sodium salts with acid chlorides or anhydrides.⁶⁸ Potassium phenyldiazotate reacts with alcohols in the cold to form diazo ethers.⁶⁹

Thiophenols and thionaphthols react with diazo compounds to form diazo thio ethers, $\text{ArN} = \text{NSAr}$.⁷⁰ These compounds are more stable than the corresponding O-ethers. Diazo thio ethers are also obtained through the reaction of aliphatic mercaptans with diazo compounds.⁷¹ Aromatic diazo thio ethers are usually more stable than aliphatic diazo thio ethers. Xanthates give with diazo compounds thio esters that are often explosive.

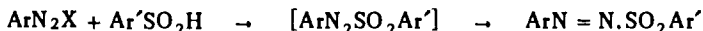
Diazo Cyanides, Sulfones, and Sulfonates

Diazo cyanides are formed when the solution of an alkali cyanide is added to the acid solution of a diazonium salt.⁷² If the reaction is carried out in the presence of some free alkali, a molecular compound of the diazo cyanide and free diazonium hydroxide is obtained.⁷³

Diazo cyanides exist in two isomeric forms, the *cis* and the *trans*. The former is obtained in the cold, but gradually changes to the *trans* isomer, the more rapidly the higher the temperature. The transformation takes place readily in alcoholic solution.⁷⁴ The *cis* isomer gives an aromatic nitrile when heated in solution in the presence of copper powder. Diazo cyanides have the ability to combine with one molecular equivalent of hydrocyanic acid.

Metallic sulfites, Me_2SO_3 , in neutral or slightly alkaline solution, react with diazo compounds forming *diazo sulfonates*, $\text{ArN}_2\text{SO}_3\text{M}$. Diazonaphthalenes form an exception and are converted almost completely to azonaphthalenes when treated with sulfites.⁷⁵ Best yields of the sulfonates are obtained by carefully controlling the pH. The sulfite must be in slight excess, and the solution should be as concentrated as possible.⁷⁶

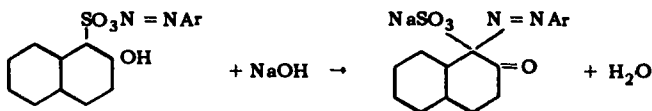
Arylsulfinic acids react with diazo compounds, apparently first forming a diazonium sulfinate, which usually undergoes rearrangement to a diazosulfone:⁷⁷



Diazo compounds give insoluble sulfonates by reaction with a number of aromatic sulfonic acids:⁷⁸

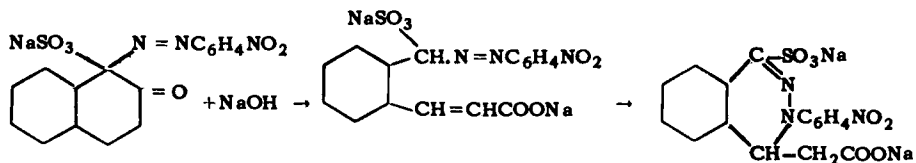


Aryldiazo-2-naphthol-1-sulfonates undergo transformation to hemi-quinoid compounds by the action of alkalis:



These compounds are hydrolyzed by acids to azo derivatives of β -naphthol. The transformation takes place with diazo compounds derived from *ortho*, *meta* and *para*-nitroaniline, 2,4-dinitroaniline, 4-chloro-2-nitroaniline, 4-nitroaniline-2-sulfonic acid, 2,6-dibromo-4-nitroaniline, 3-nitro-4-toluidine, and *p*-aminoazobenzene. It fails to take place with diazo compounds derived from aniline, toluidines, tribromoaniline, sulfanilic acid, dichloroaniline, *p*-aminoacetanilide, anthranilic acid and α - and β -naphthylamine.

When sodium hydroxide is added to the solution of the hemiquinoid salt obtained from a *p*-nitro aryl diazonium compound, disodium-4-nitroaryl-3,4-dihydrophthalazine-1-sulfonate-4-acetate is formed:⁷⁹



The intermediate compound may be obtained when cold caustic is allowed to react for a minute with the hemi-quinoid substance derived from the *o*-nitrophenyldiazo compound, while the dihydrophthalazine is obtained if the reaction is allowed to continue for two days.⁸⁰

Diazoamino Compounds

Diazonium compounds react with primary and secondary amines to form diazo-amino compounds, also termed *triazens*:



The reaction with primary aromatic amines is carried out by mixing a concentrated aqueous solution of the diazonium compound with an aqueous solution of the hydrochloride of the amine, and adding sodium acetate. Reaction may also be brought about by adding sodium acetate to a mixture of a solution of the diazonium compound and an alcoholic solution of the amine.

An aromatic amine may be made to react with its own diazo compound to form a diazo-amino compound by adding one equivalent of sodium nitrite to an aqueous solution of two equivalents of the amine and one of acid.⁸¹ Alternatively, three equivalents of hydrochloric acid are added to two of the amine in aqueous solution, followed by sodium nitrite and sufficient sodium acetate to react with all of the excess mineral acid.⁸² It is essential to avoid the presence of any mineral acid in excess over that required for the generation of nitrous acid from the nitrite. Aromatic diazoamino compounds are also formed by the action of an alkali metal nitrite on a salt of a primary amine in the absence of a mineral acid.

A complex series of reactions takes place when ammonia is made to act on a diazo compound.

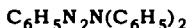
Diazoamino compounds have been used in the dye industry under the name of "rapidogens" as a source of diazonium compounds. The stability and the developing power of this class of compounds are both important considerations in the choice of the amine and diazo compounds used in their preparation. As a general rule to be observed in the choice, the more reactive the diazo compound the less basic should be the amine component.³²⁶

As an example of the procedure, the preparation of 3-chlorophenyldiazo-(2-carboxy-5-sulfophenylamine) may be cited: 184 gm of 3-chloroaniline are stirred with 360 cc hydrochloric acid of 19.5° Bé and 1200 gm ice for one hour and 100 gm sodium nitrite are added in the form of a 30% aqueous solution. The mixture is added to one prepared by mixing a solution of 330 gm 4-sulfon-2-aminobenzoic acid in 800 cc water with 300 cc 40% caustic and 300 cc 20% aqueous sodium acetate, keeping the temperature at 15 to 20°. Sufficient 20% aqueous caustic is next added slowly until the liquid becomes slightly alkaline, the mixture is agitated overnight, and is finally heated to 55 to 60°. After diluting the reaction mixture to 9000 cc with water, 450 gm of sodium chloride are added, the liquid is well agitated for a time in order to dissolve the salt, and the precipitated diazoamino compound is filtered, washed and dried at 95° under vacuum.³²⁷

Primary aliphatic amines tend to form bisdiazo compounds by reaction with two molecular proportions of the diazo compound.⁸³ The monodiazo compounds may be prepared, however, by carrying out the reaction in aqueous solution in the presence of ether or other solvent immiscible with water, the solvent dissolving the monodiazo compound as rapidly as it is formed.⁸⁴

Bisdiazoamino compounds are not formed from aromatic primary amines and diazo compounds. Compounds of this type may be prepared, however, through the reaction of the monodiazoamino compounds with a methanolic solution of the diazo compound in the presence of sodium methylate.

Only a few diazodiarlamines are known. Diphenylaminodiazobenzene,



is obtained through the reaction of diazobenzene with diphenylamine.

Aromatic diazo alkyl amino compounds are formed by the reaction of alkyl magnesium halides with aromatic azides:⁸⁵



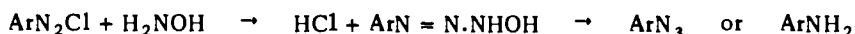
The nitrogen atom with a double bond in diazoamino compounds is always adjacent to an aromatic residue.⁸⁶ If a diazo compound is free to combine with either an amino or an imino group, as in amidines, it combines preferentially with the amino group.⁸⁷ The same diazoamino compound is obtained when diazo benzene reacts with *p*-toluidine, as when diazo-*p*-toluene reacts with aniline.⁸⁸ Occasionally the reaction of a diazonium compound with an amine may consist of an interchange of the diazonium and the amino groups.⁸⁹ Such an interchange appears to take place when *m*-xylidine reacts with a β -naphthyldiazonium salt, the final product of the reaction being *m*-xylene-4-azo- β -naphthylamine. The reaction of some amines with azo compounds may result in the formation of the isomeric amino azo compound. Aminonaphthalenes yield the

aminoazo compounds almost exclusively; alkylated aromatic amines also yield the aminoazo compound if the para position in the aromatic nucleus is not occupied by a substituent.⁹⁰

When a solution of a diazoamino compound is acidified, the amine and the original diazo compound are regenerated.

The principal product of the reaction of a *sulfonamide*, RSO_2NH_2 , with a diazo compound, RN_2X , is an aryl azide, ArN_3 , although the reaction is complicated by the simultaneous formation of a diazosulfone.⁹¹

Hydroxylamine reacts with diazo compounds forming first a hydroxydiazoamino compound which gives rise finally to a triazine or to the original aromatic amine, depending upon the experimental conditions:⁹²



The azide is formed as the original product when the solution of the diazo salt and hydroxylamine are brought together in neutral or slightly acid solution, and the mixture is then made alkaline.⁹³ On the other hand, the amine is formed in high yield when the solution of the diazo salt is added to an alkaline solution of hydroxylamine.

Hydroxydiazoamino compounds of the anthraquinone series are stable. Removal of the elements of water from 1-(hydroxydiazoamino)anthraquinone, for example, required treatment with acetic anhydride; the resulting product is an anthraquinone-1-azide.⁹⁴

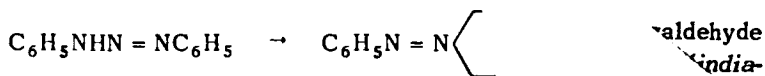
Oximes are capable of reacting with diazo compounds, two molecular proportions of the former combining with one of the latter.⁹⁵

Diazo compounds combine with N-alkyl or N-aryl hydroxylamines, RNHOH , to form stable hydroxydiazoamino compounds, $\text{ArN} = \text{N.N(OH)R}$. These compounds are decomposed by strong acids.⁹⁶

Hydrazine and aromatic hydrazines react in a complicated manner with diazo compounds. Phenylhydrazine, for example, reacting with *m*-diazobenzoic acid, gives a phenyl azide, *m*-carboxyphenylazide, aniline, and *m*-aminobenzoic acid.⁹⁷ *Acylated hydrazines* yield stable diazohydrazides which form tetrazoles on treatment with alkalis.⁹⁸ The reaction of sodium nitrite with phenylhydrazine results in the formation of phenylazide.⁹⁹

Cyanamide, dicyanodiamide, guanidine and other similar bodies are also capable of combining with aromatic diazo compounds to form the corresponding diazoamino compounds.¹⁰⁰ Such compounds are used as components in rapidogen type dyes. The compounds derived from dicyanodiamide, $\text{CN.NHC}(\text{:NH})\text{NHN}_2\text{Ar}$, are converted to arylcyanoguanidines, $\text{CNNHC}(\text{:NH})\text{NHAr}$, on treatment with moist hydrogen chloride, or by heating with acid in a high boiling solvent. Benzenediazocyanamide, $\text{C}_6\text{H}_5\text{N}:\text{N.NHCN}$, has been obtained in the form of its potassium salt by heating potassium cyanide with phenylazide in alcoholic solution.

Diazoamino compounds undergo molecular rearrangement to aminoazo compounds through the prolonged action of an amine containing some amine hydrochloride:

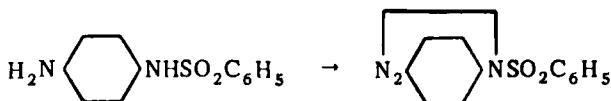


It is probable that the diazoamino compound first under-
 amine and the diazo compound, and these then combine
 compound.¹⁰¹ The amino group in the resulting aminoazo
 the *para* position, although conditions are known under which
 ortho coupling occurs.¹⁰² The rearrangement fails to occur if a substituent is
 present in the *para* position.

Aminoazo compounds form two isomeric series of salts, a yellow, unstable
 type, and one of dark violet color and stable, the latter probably having a quin-
 oid structure.¹⁰³

Diazoimines

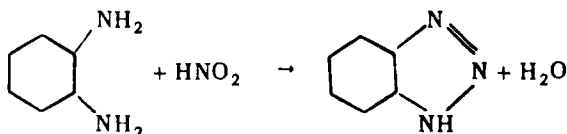
An amido group in the *para* position with respect to the diazo group in an
 aromatic compound, if sufficiently activated, interacts with the diazo group to
 form a diazoimine. A diazoimine is obtained, for example, on diazotizing *p*-amino-
 benzenesulfonamide:¹⁰⁴



Diazoimines are yellow, explosive, monomeric solids. In many of their prop-
 erties they resemble diazo oxides, but are less stable and more reactive.

Triazoles, Triazines, and Tetrazoles

Triazoles are internal diazoamino compounds that result through the diazo-
 tization of ortho diamines:¹⁰⁵

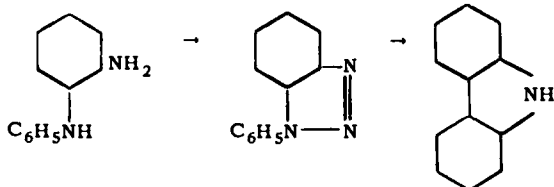


The reaction takes place under a wide range of temperature and acidity condi-
 tions. The triazoles usually precipitate out as colorless solids, unless they
 contain groups rendering them water soluble. The reaction is of general applica-
 bility in the benzene, naphthalene and anthraquinone series. It is applicable
 to compounds in which the amino group is secondary or is acylated.

Triazoles are amphoteric bodies reacting both as weak acids and weak bases.
 The triazol ring is quite stable and cannot be ruptured to regenerate the diazo-
 nium salt and the amine.

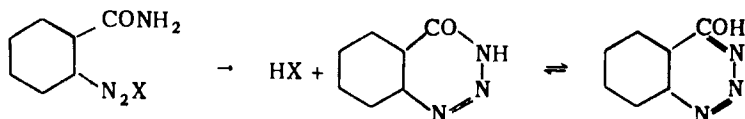
1-Phenyltriazole, which results from the diazotization of *o*-aminodiphenylamine, is
 converted to carbazole on heating at 360°:¹⁰⁶

aminoaz
the a
C₆H₅



Substituted carbazoles may be prepared by this method from substituted *o*-aminodiphenylamines. The preparation of the intermediate triazole presents no difficulty, but its conversion to carbazole by heating is by no means uniformly satisfactory. The carbazole is obtained in good yield, as a rule, when substituents are present. Naphthocarbazole can also be made by this method. The method is applicable to anthraquinone derivatives

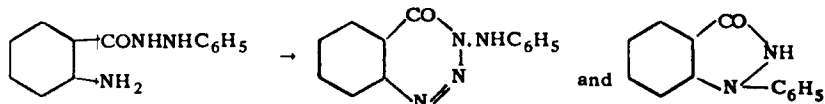
Benzotriazines are obtained as a result of the formation of internal azoamino compounds from *o*-diazobenzamide:¹⁰⁷



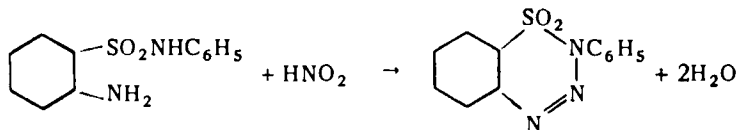
Benzotriazines are formed, and precipitate out at once, when *o*-aminobenzamide or its derivatives are diazotized. The reaction is of general applicability.

N-Aryl- or *N*-alkyl-*o*-aminobenzamides afford 3-substituted benzotriazines.¹⁰⁸ *o*-Aminobenzhydrazides afford 3-substituted benzotriazines. *o*-Aminobenzhydrazide, treated with two equivalents of nitrous acid, gives 3-amino-4-keto-3,4-dihydro-1,2,3-benzotriazine.¹⁰⁹

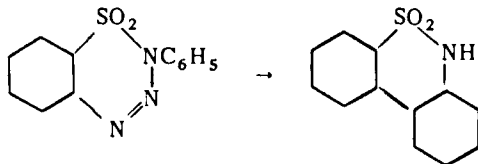
The diazotization of α -(*o*-aminobenzoyl)- β -phenylhydrazine results in the formation of a mixture of 3-anilino-4-ketodihydrobenzotriazine and 1-phenylindazolone, the latter being formed by loss of the diazo nitrogen atoms:¹¹⁰



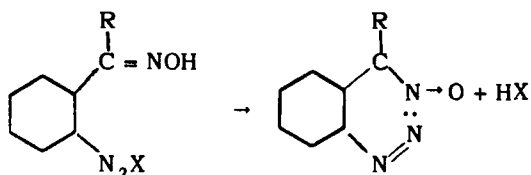
o-Aminosulfonamides also yield triazines when diazotized.¹¹¹ The formation of 1-phenylbenzenesulfontriazine proceeds in the cold on diazotization of *o*-aminobenzenesulfanilide:



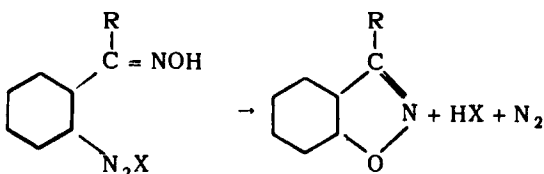
Diphenylsulfam is formed when 1-phenylbenzenesulfontriazine is boiled with copper powder:



Diazotization of the lower melting isomers of oximes of *o*-aminobenzaldehyde and its derivatives also results in the formation of triazines, the "indiazones";¹¹²

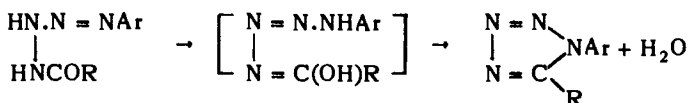


The higher melting isomers of the oximes, *h*-oximes, give 3-substituted *indoxazenes*:



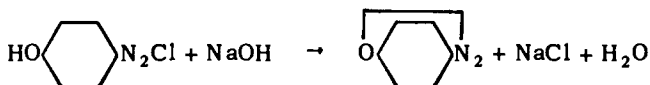
o-Aminobenzaldoxime gives 1,2,3-benzotriazine-3-oxide in poor yield, but substituted triazines are obtained in better yield from 3,5-dimethyl- and 3,6-dichloro-2-aminobenzaldoxime.

1,2,3,4-Tetrazoles are formed when diazoaryl mono- and diacylhydrazides are treated with alkali:



Diazo Oxides

Aromatic amines having a hydroxyl group in *ortho* or *para* position may yield a hydroxydiazonium salt on diazotization; when treated with caustic, these are converted to diazo oxides:



Many *o*- and *p*-hydroxy amines are converted to diazo oxides directly on diazotization, the oxides separating as precipitates. Internal diazonium sulfonates are obtained on diazotization of aminophenol- and aminonaphtholsulfonic acids, except when the amino and hydroxyl groups are adjacent, when diazo oxides are formed. Diazo oxides are obtained from aminophenolcarboxylic acids regardless of whether the hydroxyl group is in the *ortho* or *para* position to the amino group.

Diazo oxides may be formed also when amino compounds containing halogen atoms, or nitro groups in *ortho* or *para* position are diazotized, the process in-

volving loss of the halogen atom, or the nitro group, and its replacement by a hydroxyl group. The tendency toward the formation of diazo oxides is occasionally so strong, the oxide is formed by the elimination of a methyl group from a methoxyl group. This occurs, for example, when 2,6-dinitro-*p*-anisidine is diazotized.¹¹³

Diazonium Perhalides

Diazonium halides combine with two atoms of halogens to form perhalides; benzenediazonium bromide, for example, adds two atoms of bromine to form benzenediazonium perbromide, $C_6H_5N_2Br_3$. The three halogen atoms in these compounds may be alike or dissimilar. Diazonium perhalides are stable, crystalline compounds.¹¹⁴

Benzenediazonium perbromide is readily obtained by adding a solution of bromine in hydrobromic acid to an aqueous solution of benzenediazonium nitrate. The compound is converted to benzenediazonium bromide on repeated washing with ether. It decomposes in moist air, giving phenol and tribromophenol. It behaves in many respects as a mixture of bromine and benzenediazonium bromide.¹¹⁵

Diazonium perhalides react with ammonia to form aromatic azides.¹¹⁶

Halogenation, Nitration, and Sulfonation of Diazo Compounds

The high reactivity of the diazo group in aromatic diazo compounds makes it impossible, as a rule, to carry out the halogenation, nitration and sulfonation of the aromatic groups in these compounds, without affecting the diazo group. It is sometimes possible, however, to carry out such reactions in strongly acid solution, providing the diazo group is sufficiently stable, and substitution proceeds with sufficient ease. Diazo oxides are among compounds which can be subjected to chlorination and other substitution reactions. Diazo compounds derived from *o*-aminonaphtholsulfone and *o*-aminocarboxylic acids also satisfy the condition.

Replacement of Substituents

A replacement of substituents present in diazo compounds may take place under certain conditions. 2,4-Dinitrodiazobenzene, treated with aqueous alkalis, is converted to 4-nitro-2-hydroxydiazobenzene, which changes immediately to 4-nitrobenzene-1,2-diazo oxide.¹¹⁷ Diazotization of amines having negative groups in ortho or para position generally results in the formation of diazo oxides if other negative groups are present in the aromatic nucleus.¹¹⁸ A nitro or methoxy group may be eliminated if it is in ortho position to the diazo group, and at the same time adjacent to a nitro group.¹¹⁹ Nitronaphthalenediazonium salts are more susceptible to hydrolytic cleavage than the corresponding benzenoid compounds.¹²⁰ The sulfonic group is exchanged for a hydroxyl when diazo compounds derived from 2-naphthylamine-1,5,7-trisulfonic acid and 1-naphthylaminedisulfonic acid are subjected to the action of aqueous sodium carbonate.¹²¹ Many cases of exchange of halogen atoms for hydroxyl have been

reported.¹²² A nitro group in ortho position may be replaced with chlorine on diazotizing polynitroanisidines in hydrochloric acid solution.¹²³ The formation of diazo oxides from nitro amines is of considerable practical importance, because of the ability of these oxides to form stable coordination compounds with metallic salts, a property which is utilized in the synthesis of mordant dyes.

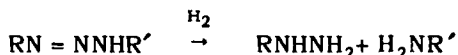
Occasionally an interchange between the anion attached to the diazo group and an element or group present in the para position in the aromatic nucleus has been observed. Such an exchange takes place when *p*-chlorobenzenediazonium thiocyanate is dissolved in ethanol containing a drop of aqueous hydrochloric acid:¹²⁴



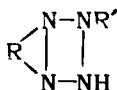
Chlorobenzenediazonium bromides also undergo a similar exchange.¹²⁵ The interchange takes place most readily when more than one bromine atom is present in the aromatic nucleus. The tendency for interchange is so strong in pentabromobenzenediazonium chloride that it has been impossible to obtain this compound free from nuclear chlorine.

Reduction of Diazo Compounds

Aromatic diazo sulfonates may be reduced to the corresponding hydrazine-sulfonic acids with sodium bisulfite or sulfur dioxide. The free aromatic hydrazine may be obtained by hydrolysis of the sulfonate.¹²⁶ Aromatic diazo compounds may be reduced to hydrazines with zinc dust and hydrochloric acid. Nuclearily substituted diazo compounds, naphthyl- and ortho- and meta-nitrophenyldiazonium compounds can be successfully converted to the corresponding hydrazines by this method.¹²⁷ Zinc dust and acetic acid may also be employed for the purpose. Diazoamino compounds may be reduced to hydrazines with zinc dust and acetic acid in alcoholic solution:¹²⁸



The reduction of *ortho* diazo azobodies results in the formation of diazohydrides which show no basic character and may be boiled unchanged with stannous chloride and hydriodic acid. Bromine converts these compounds to the perbromide of the original diazo bodies. They are apparently ring compounds of the type

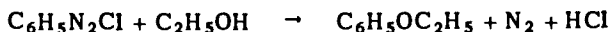


2,2'-Tetrazodiphenyl and its derivatives, subjected to the action of reducing agents, are converted to carbazoles in considerable yield.¹²⁹

ide, cuprous sulfate and zinc oxide have been employed as promoters in this reaction. Cupric oxide is claimed to give generally satisfactory results.¹³² The utility of these catalysts is limited, however, and they may even have an adverse effect in some instances.¹³³

The use of sulfuric acid in the preparation of the diazo compound rather than hydrochloric acid, is of advantage, since the use of the latter acid involves the risk of replacement of bromine atom or nitro groups that may be present in the aromatic group with chlorine. Such an exchange takes place with polybromodiazocompounds having bromine atoms in the para and ortho positions.¹³⁴ An exchange of the nitro groups for chlorine has been observed in the naphthalene series. Apparently no halogen exchange occurs with diazonium fluorides. The use of diazo nitrates offers no advantage and may result in the formation of nitrated products.

The reaction of an alcohol with a diazo compound may result in the formation of an ether:¹³⁵



The replacement reaction and ether formation often proceed simultaneously. The tendency toward the formation of ether decreases with increasing molecular weight of the alcohol employed,¹³⁶ although there seems to be no particular advantage in the use of an alcohol other than ethanol. Polyhydric alcohols seem to give ethers exclusively.¹³⁷ Nitrosoacylanilides give fair yields of the deamination product in methanol, but in the presence of sulfuric acid the phenol ether is the main product.³⁰²

The direction in which the reaction proceeds is determined to a great extent by the character of the substituents present in the aromatic nucleus. Negative substituents favor the replacement of the diazo group with hydrogen. The effect of substituents in the *ortho* position is the most marked, that in the *para* position the least marked.¹³⁸ The replacement reaction takes place in satisfactory manner with nitrated diazo compounds, both in the benzene and naphthalene series.¹³⁹ Hydroxyl,¹⁴⁰ carboxyl and acyl groups and halogens also exert a marked effect. Ether formation is suppressed in the reaction of many diazo compounds with negative substituents, especially if ethyl alcohol is employed as the reducing agent. When the diazo compound derived from *o*-aminobenzoic acid is treated with anhydrous ethanol, only replacement of the diazo group with hydrogen occurs, while with the diazo compound derived from *p*-aminobenzoic acid, ether formation is the predominant reaction. A methyl group present in the *ortho* or *meta* position suppresses the replacement reaction entirely, while one in the para position favors this reaction. The action of a sulfonic group is similar to that of a methyl group.

The direction in which the reaction proceeds may be influenced by the pressure under which the reaction is carried out. Thus, when *p*-diazobenzenesulfonic acid is made to react with methanol under reduced pressure, benzene sulfonic acid is the only product, while under atmospheric pressure, both benzenesulfonic acid and anisolsulfonic acid are formed, and under 30 lb pressure only the latter compound is formed.

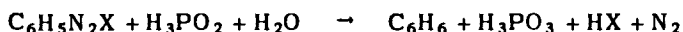
The reaction of boiling methanol with diazohydroxides or diazotates results in the replacement of the diazo group with hydrogen.¹⁴¹

Salts of diazonium compounds with naphthalene-1,5-disulfonic or 2-naphthol-1-sulfonic acid may be reduced smoothly by treatment with ethanol and zinc or copper at room temperature. The yields are usually of the order of 90% and the method is claimed to be of general applicability.¹⁴²

Deamination of aromatic amines has been carried out by boiling the amine with an alcoholic solution of ethyl or amyl nitrite.

Reduction by Use of Hypophosphorous Acid

The diazo group in aromatic compounds may be effectively replaced with hydrogen by reduction with hypophosphorous acid:¹⁴³



This is an excellent method of general applicability. Five molecular equivalents of hypophosphorous acid are generally required per mole of diazo compound for satisfactory results, and occasionally it is necessary to use as much as fifteen molecular equivalents of the acid.

The procedure is quite simple: A 30 or 50% aqueous solution of hypophosphorous acid cooled to 0° is added to the solution of the diazo compound, also cooled to the same temperature, and reaction is allowed to proceed at 0° to 5°. Reduction is generally complete in the course of twenty-four hours.¹⁴⁴ The reaction proceeds satisfactorily with diazonium chlorides.

The method gives results at least equal to those obtained by the alcohol method, and will often give satisfactory results in cases where the alcohol method fails.

Reduction with Alkaline Formaldehyde and other Reagents

Alkaline formaldehyde solution is a very satisfactory reagent for the reduction of diazo compounds derived from benzene and its homologs, and from aromatic amino ethers.¹⁴⁵ The method is not applicable to alkali-sensitive diazo compounds, such as compounds having a halogen atom in the *para* or *ortho* position in the aromatic nucleus. The method gives more satisfactory results than the ethyl alcohol reduction procedure with diazo compounds bearing positive substituents. Yields of replacement product from alkoxy and aryloxy-diazo compounds range 50 to 75%; the yield from *m*-methylphenyldiazonium salts is about 80%.

Replacement of the diazo group with hydrogen may be effected by the action of cuprous oxide in methanol, or in a mixture of sulfuric and acetic acids.³⁰⁶ Replacement has been brought about by the action of copper or zinc powder in alcoholic suspension at room temperature on stabilized diazonium salts. Yields of 90% have been obtained by this method from diazo compounds derived from amidines, nitroanilines, *m*-phenylenediamine, benzidine and α - and β -naphthylamines.³⁰⁷ In the *Angeli method*, cuprous salts formed in situ from sodium hypophosphite and copper sulfate are employed.³⁰⁸ In the *Körner-Contardi method*,³⁰⁹

which is limited to negatively substituted diazo compounds, cupric oxide is used, since unsatisfactory results are obtained with this class of compounds with cuprous salts.

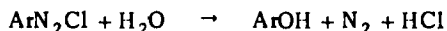
Diazo groups may be replaced with hydrogen also by reduction with stannous chloride,¹⁴⁶ or with alkaline sodium stannite.¹⁴⁷ Reduction with sodium stannite is not applicable to *n*-diazotates that are decomposed in alkaline media. iso-Diazotates are unaffected by alkaline sodium stannite. Formic acid, hydroquinone,¹⁴⁸ and alkaline sodium sulfide¹⁴⁹ have also been employed for the purpose. Ammoniacal copper sulfate treated with sulfur dioxide has been employed for the replacement of the diazo group in 1,4-, 1,5- and 1,8-diazonaphthalenesulfonic acids with hydrogen.¹⁵⁰

The reduction of diazo compounds with sodium sulfite or stannous chloride leads to the formation of hydrazines.¹⁵¹ Since certain oxidizing agents may cause the replacement of the hydrazine group with hydrogen, the reaction offers an indirect means for replacing the diazo group with a hydrogen atom. The oxidation of the hydrazine is usually effected with hot aqueous cupric sulfate, ferric chloride or potassium chromate.¹⁵² It is desirable to convert hydrazine hydrochloride to the free base before subjecting it to the action of the oxidizing agent in order to avoid the formation of a chlorinated compound.

Replacement of the diazo group with hydrogen is of most interest in the naphthalene series, as it affords the means for the preparation of various nitronaphthols, dinitronaphthalenes, and naphthalenesulfonic acids not easily obtainable by other methods.¹⁵³

Replacement of the Diazo Group with Hydroxyl

Replacement of a diazo group in an aromatic compound with a hydroxyl group takes place through the reaction of the diazo compound with water:¹⁵⁴



The reaction proceeds slowly at ordinary temperature, but is accelerated by heat. The yield of phenolic compound would appear to be greater, the greater the dilution of the solution in which the reaction is carried out.¹⁵⁵ Phenyl-diazonium chloride is readily converted to phenol by boiling water. Conversion to phenol does not take place readily, however, with diazo compounds containing amino or other negative groups. With the more resistant diazo compounds it may be necessary to use aqueous sulfuric acid, or a solution of sodium sulfate in aqueous sulfuric acid, and to heat the mixture of the diazo compound with the solution to 135-145°. ¹⁵⁶ Rapid conversion to the phenolic body is desirable in order to avoid as much as possible the coupling reaction between the phenol and the unreacted diazo compound. It is best, for this reason, to add the solution of the diazo compound to the heated acid solution. The replacement of the diazo group with hydroxyl in the more resistant compounds may also be brought about by adding the compound dropwise to a boiling aqueous solution of copper sulfate. The diazo compound may be decomposed at the time of its formation, with replacement of the diazo group with hydroxyl, by adding sodium nitrite

solution to a boiling solution of the amine salt. Aminoanthraquinones can be converted to hydroxyanthraquinones by this procedure.¹⁵⁷ Diazobenzofurans have been converted to hydroxydibenzofurans by mixing with syrupy phosphoric acid and dropping into a flask through which a current of superheated steam is passed.¹⁵⁸

One diazo group in 3-methoxy-4,4'-tetrazodiphenyl is replaced with hydroxyl on treatment with hot water, giving 3-hydroxy-3-ethoxy-4-diazodiphenyl. The ortho substituent protects the remaining diazo group in this instance, though such protection is not general.¹⁵⁹ Treatment with hot water causes the conversion of 1-diazonaphthalene-4-sulfonic acid largely to the azo dye 1-hydroxy-2,1'-azonaphthalene-4,4'-disulfonic acid.¹⁶⁰

It has been impossible to replace the diazo group with a hydroxyl group in certain diazo compounds. 3,3'-Dimethoxy- and 3,3'-dichloro-4,4'-tetrazodiphenyl and 1-naphthyl-1,2,2'-tetrazonium sulfate are among such compounds.¹⁶¹

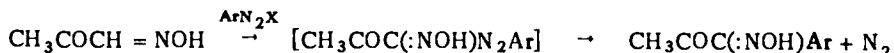
Replacement of the Diazo Group with Alkoxy, Aryloxy, and Acyl Groups

The reaction of diazonium salts with alcohols may result in the replacement of the diazo group with an alkoxyl group.¹⁶² Chlorotoluenediazonium sulfate, for example, boiled with ethyl alcohol gives chlorocresol ethyl ether, and cumene- and tetramethylbenzenediazonium sulfate yield the corresponding ethoxy compounds. Both diazo groups in tetrazo compounds such as 4,4'-tetrazo-3,3'-ditolyl, are replaced with the ethoxyl group by this treatment. The internal diazonium salts obtained from *o*-toluidinesulfonic- and anilinedisulfonic acids also give ethoxy compounds on boiling with ethanol.

Phenols react with diazonium salts in the absence of water to form aromatic ethers by elimination of the diazo group.¹⁶³ The yields of diaryl ethers are generally very low, however, and the method has little preparative value.

The diazo group may be replaced with the acetoxyl group by boiling the diazo compound with glacial acetic acid or acetic anhydride.¹⁶⁴ The reaction is most readily carried out with easily isolated diazo compounds, such as those of high molecular weight.¹⁶⁵ Diazonium fluoborates have been employed for the purpose successfully.¹⁶⁶

Aldoximes in which the group $\text{CH}=\text{NOH}$ is adjacent to a carbonyl group react in alkaline solution with diazobenzene and certain other aromatic diazo compounds to form the monoxime of an aliphatic aromatic diketone:¹⁶⁷

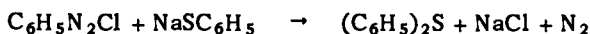


Replacement of the Diazo Group with Thio and Other Sulfur-Containing Groups; the Leuckart Reaction

Aromatic sulfides and disulfides are formed when aromatic diazo compounds are heated with an alcoholic solution of alkali metal sulfides.¹⁶⁸ The reaction proceeds satisfactorily with diazo compounds derived from anthranilic acid. In the reaction of aromatic diazonium chlorides and ammonium sulfide a reddish yellow precipitate forms first, which decomposes with explosive violence if not cooled effectively.

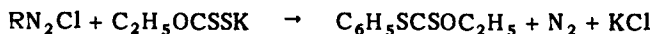
As an example of the *procedure*, the preparation of thiosalicylic acid may be mentioned: 100 gm sodium sulfide and 29 gm flowers of sulfur are heated with water and the solution obtained is poured into a mixture of 540 cc water, 500 gm ice and 227 gm of 33% aqueous caustic; the resulting liquid is cooled to 0° and the diazo solution prepared from 137 gm anthranilic acid is added slowly. The liquid is then allowed to warm up to 15°, and is agitated overnight. When the evolution of nitrogen ceases, 300 gm of iron turnings, 50 gm sodium sulfate and 540 gm of hydrochloric acid are added, and the mixture is heated slowly to 95° and is maintained at this temperature for five hours. The thiosalicylic acid formed is isolated by an appropriate method.³²⁸

Aromatic sulfides result through the reaction of diazonium chlorides with sodium mercaptides:

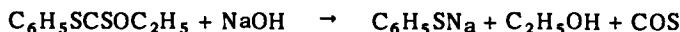


A sulfur to carbon bond may be established also through the reaction of certain sulfur containing compounds, such as thiosulfates, xanthates etc., with diazo compounds.

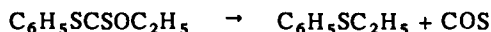
*Leuckart's reaction*¹⁶⁹ makes use of the interaction of diazo compounds with alkali metal xanthates:



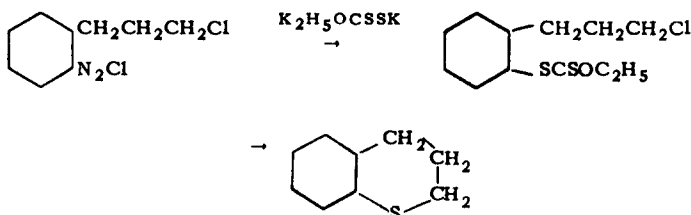
The procedure is to add an ice-cold solution of the alkali metal xanthate to the similarly cooled solution of the diazo compound. The aromatic xanthate obtained is converted to a thiol by treating with alcoholic caustic:



The xanthate is converted to a thioether when heated:



The diazo compound derived from *o*- γ -chloropropylaniline, mixed with potassium xanthate and slowly heated to 70°, gives a thiochroman:¹⁷⁰



The diazo group may be replaced with a sulfinic group, $-\text{SOOH}$, by saturating the diazonium sulfate in dilute sulfuric acid solution with sulfur dioxide and adding copper powder. The sulfinic acid is obtained in low yield by this method from the diazo compound derived from *m*-toluidine.¹⁷¹ The sulfinic acid may be isolated by precipitation with a ferric salt.¹⁷²

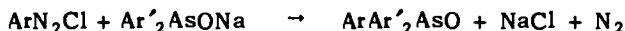
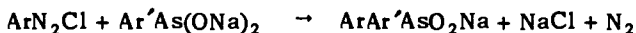
The Bart Reaction

The diazo group in an aromatic diazo compound may be replaced with the arsonic group by reaction with sodium arsenite in alkaline solution:



This method is due to Bart.¹⁷³ The reaction is catalyzed by copper powder, copper salts, metallic nickel or cobalt and their salts. In a modification of the method, a reducing agent is employed in conjunction with a copper salt.¹⁷⁴ Sodium carbonate is often employed as a buffering agent and generally brings about a decided increase in the yield of arsonic acid.¹⁷⁵ Other compounds which act as buffering agents also cause an increase in yield. It has been claimed that the best yields are obtained when the reaction is carried out in neutral solution, without the use of a catalyst.¹⁷⁶ If the reaction is carried out in acid solution, the yields are low unless the aromatic nucleus contains strongly negative substituents, such as nitro groups, in the ortho or para positions.

Aromatic arsinic acids and arsine oxides may be prepared by this method by use of the sodium salt of an aromatic arsonic or arsinic acid in place of sodium arsenite:



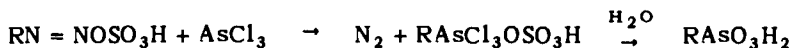
o-Nitrodiphenylarsinic acid has been prepared in good yield through the reaction of *o*-nitrobenzenediazonium chloride with phenylarsenous oxide in a solution buffered with acetic acid and sodium acetate.¹⁷⁷

In general, diazo compounds with substituted aromatic groups give good yields of arsonic acids by Bart's method. Diazo compounds in which the aromatic nucleus carries alkyl substituents also give good yields of arsonic acids. Yields of arsonic acid are low from diazo compounds derived from *o*-, *m*- and *p*-aminobenzyl alcohols. *o*-Nitrobenzenediazonium chloride gives an excellent yield of arsonic acid; good yields are also obtained from the 2,4-dinitro compound, moderate yields from the *p*-nitro, and poor yields from the *m*-nitro compound. The reaction fails to take place with diazo compounds derived from 2-bromo-6-nitro anilines. Diazo compounds derived from 2-hydroxy-4-nitro-5-alkylaniline give arsonic acids in yields decreasing with increase in the length of the alkyl chain. In general, the presence of halogens in the aromatic nucleus does not influence the ease with which the reaction proceeds. Diazo compounds with *hydroxyl* groups in the ortho and para position give arsonic acids in 35 to 90% yield, while a diazo compound with hydroxyl in the meta position fails to react. *Alkoxy* groups appear to have an effect comparable with that of hydroxyl groups. The presence of a basic group in an alkoxy side chain decreases the yield, and may even prevent the formation of an arsonic acid. *Carboxyl* groups in *ortho* and *para* position have no unfavorable effect. *Keto* groups apparently exert a favorable effect, while *aldehyde* groups cause a decrease in yield.

Scheller Reaction

Arsonic acids result when primary aromatic amines dissolved in methanol or glacial acetic acid are diazotized in the presence of arsenic trichloride and a

trace of cuprous chloride, and the reaction product is treated with water and sodium hydrosulfite, or is subjected to steam distillation:¹⁷⁸



The *general procedure* is as follows: A mixture of a solution of 0.1 mole of the amine in 250 cc of absolute alcohol with 10 gm of sulfuric acid and 28 gm of arsenic trichloride is cooled to 0° and is diazotized with the calculated amount of sodium nitrite dissolved in the least possible quantity of water. After completion of the diazotization, 1 gm of cuprous bromide is added, the mixture is agitated vigorously and heated to 60° until the evolution of nitrogen ceases. The mixture is finally subjected to steam distillation; the arsonic acid obtained is purified by recrystallization.

Arsonic acids have been obtained by this method from *p*-nitroaniline and *p*-aminoacetophenone. Better yields of arsonic acids have been obtained in many instances by this method than by the Bart method. The improvement in yield is especially marked with amines having negative substituents in the *meta* position. The reaction is not applicable to metanilic acid, 3,5-xyldine and 2,6-xylidene.

Replacement of the Diazo Group by Halogens

The replacement of the diazo group with a halogen may be effected simply by boiling the diazonium halides with an excess of concentrated hydrogen halide.¹⁷⁹ The hydrogen halides are often used in glacial acetic acid solution. The chloride and bromide are obtained in unsatisfactory yield by this method, but the iodo derivatives are formed in good yield.¹⁸⁰ The iodo derivative may be prepared by adding sodium iodide to a solution of the diazonium salt, preferably the sulfate, containing an excess of mineral acid, and gently warming.¹⁸¹ Replacement of the diazo group with fluorine may also be effected by heating the diazo compound with hydrofluoric acid,¹⁸² although the yields are low. Replacement of the diazo group with a chlorine or bromine atom may be accomplished by heating the double salts of the diazo chlorides or bromides with platinum tetrachloride or tetrabromide, or those with mercuric chloride or bromide.¹⁸³ The bromo derivatives may be obtained by boiling diazonium perbromides with alcohol:



Bromobenzene has been prepared by distilling a mixture of diazobenzene perbromide with sodium carbonate.¹⁸⁴

Sandmeyer's Reaction

The most satisfactory method for the replacement of diazo groups with chlorine is that originated by Sandmeyer.¹⁸⁵ The method utilizes the catalytic action of cuprous chloride in the decomposition of diazo chlorides. The primary reaction would appear to involve an interaction between the diazonium and the copper chloride ions, with the latter changing to the unreactive CuCl_4^- ion. A suggested mechanism postulates a slow ω -coordination of the terminal diazon-

ium nitrogen and copper chloride to $\text{ArN}_2\text{CuCl}_2$, followed by decomposition to ArCl . An alternative view envisions a rapid interaction of ArN_2^+ with copper chloride, resulting in the formation of $[(\text{ArN}_2)_2\text{CuCl}_2]^+$, the latter decomposing to ArCl , nitrogen and cuprous chloride.

The procedure is to add the cold solution of the diazonium halide to the solution of the cuprous chloride in concentrated hydrochloric acid at such a rate that a brisk evolution of nitrogen takes place. Vigorous reaction occurs within one or two minutes. A deep brown, sparingly soluble complex of the diazo halide with cuprous chloride, $(\text{ArN}_2\text{Cl})_3\text{CuCl}$, forms as intermediate. This undergoes decomposition with the formation of the aromatic halo compound, which separates as an oily layer. The halide may be obtained in the pure form by steam distillation.

The cuprous chloride solution may be prepared in the following manner: Fifty grams of crystalline copper sulfate are dissolved in 160 cc of water containing 29 grams of sodium chloride in solution. The liquid is warmed and 29 grams of crystalline sodium sulfite are added in portions, and the solution is boiled to expel the sulfur dioxide. On addition of 75 cc of concentrated hydrochloric acid, the cuprous chloride formed dissolves completely, giving a pale greenish brown solution.

It is important to note that the diazo chloride solution is added to the cuprous chloride solution, and not vice versa. If the cuprous chloride solution is added to the diazo chloride solution, the product obtained largely consists of a symmetrical azo compound; diaryls and phenols may also form in the reaction in that case. One half molecular proportion of the cuprous chloride is generally required for the successful conversion of the diazo compound to the halide. In some instances one molecular proportion of cuprous chloride is required for successful conversion. Stable diazo compounds, such as diazonaphthalene-sulfonic acids, require small amounts of the cuprous salt. The optimum conditions for best yields of the chloro derivative must be determined experimentally for each particular diazo compound. The reaction with diazobenzene is best carried out at 0° ; that with *o*-diazotoluene at 27° ; the optimum temperature ranges between 30 to 40° for *p*-diazotoluene, and 40 to 50° for 5-diazo-2-chlorobenzaldehyde. If the reaction is carried out below the optimum temperature, the time required for the completion of reaction is increased, and a greater proportion of azo compound is formed. In the preparation of *meta*-chlorobenzaldehyde by this method, the presence of zinc compounds causes the formation of resinous matter.

Replacement of the diazo group with a halogen is catalyzed by copper powder.¹⁸⁶ Salts of metals other than copper, including those of iron, cobalt, and zinc, form anionoid complexes with diazohalides, which are capable of decomposing in the manner of copper complexes. The rate at which Sandmeyer's reaction proceeds is influenced by substituents in the aromatic ring; the effect of various substituents in decreasing order is as follows: $p\text{-NO}_2 > p\text{-Cl} > \text{H} > p\text{-CH}_3 > o\text{-CH}_3 > p\text{-COH}_3$, the velocity of reaction decreasing from left to right.

Sandmeyer's reaction is applicable to the preparation of aromatic bromo compounds from diazo compounds. For this purpose the sulfate of the diazo compound is added to a hydrobromic acid solution of cuprous bromide, and the cuprous bromide-diazo compound complex formed is decomposed by heating.

The diazo group in certain aromatic diazo salts, especially those having negative substituents, can be replaced with halogens under appropriate conditions, in the presence of cupric salts. This is known as the *Körner-Contardi replacement reaction*.¹⁸⁷

Replacement of the diazo group with bromine may be accomplished via a mercury salt complex by heating the complex with twice its weight of potassium bromide.¹⁸⁸

The replacement of the diazonium group with iodine under the action of hydriodic acid generally proceeds well,²⁹² but diazonium compounds derived from certain amino acids, such as amino-*p*-toluic and aminoterephthalic acids, give hydroxy acids instead of the expected iodo derivative.²⁹³

Pentaiodobenzene is obtained from 2,3,4,5-tetraiodobenzenediazonium chloride, when the solution of the latter in concentrated hydrochloric acid is poured into a solution of potassium iodide and the mixture is diluted with ice water.²⁹⁴

β -Iodoanthraquinone and 2-methyl-1-iodoanthraquinone have been obtained from the corresponding diazonium chlorides in aqueous solution by the action of potassium iodide.²⁹⁵

The diazo group in nitrobenzenediazonium salts is best replaced with iodine by adding a solution of iodine in aqueous potassium iodide to a solution of the diazonium compound in a large excess of concentrated sulfuric acid.²⁹⁶

Replacement of the Diazo Group with Fluorine

Diazonium fluorides fail to give aryl fluorides when heated alone or in aqueous solution in the presence of cuprous salts.¹⁸⁹ It is possible to obtain the fluoro compound, generally in low yield, by heating the diazo compound with hydrofluoric acid. Fluorobenzene has been obtained in excellent yield by dissolving aniline in anhydrous hydrofluoric acid in an iron vessel, diazotizing at 5° with sodium nitrite, then warming to 30 to 40°. ¹⁹⁰ α -Fluoronaphthalene has been prepared by a similar method.¹⁹¹

Benzenediazopiperidide, $C_6H_5N_2NC_5H_{10}$, which may be readily obtained as a precipitate by mixing solutions of benzenediazonium chloride and piperidine, reacts vigorously with hydrogen fluoride to give fluorobenzene.

The most satisfactory method for the replacement of the diazo group with fluorine is the thermal decomposition of diazonium fluoborates (*Balz-Schiemann reaction*).¹⁹²



In many instances satisfactory results are obtained by carrying out the diazotization in the presence of fluoboric acid, $HBrF_4$, and treating the fluoborate formed with copper powder.²⁹⁷

Fluoboric acid is prepared by adding 18.4 parts by weight of boric acid slowly and with continuous stirring to 45 parts of 45 to 52% aqueous hydrofluoric acid. The reaction may be carried out in a vessel constructed of copper, lead or silver, cooled in ice water.

Copper powder may be prepared by adding 35 parts by weight of zinc powder to a solution of 100 parts copper sulfate pentahydrate in 350 parts water. The precipitated metal is filtered, washed with water, treated with 5% hydrochloric acid in order to dissolve the excess zinc powder; it is again washed with water, and is kept in a closed container.²⁹⁸

Replacement of the Diazo Group with the Cyano and Miscellaneous other Groups

The diazo group in an aromatic diazonium compound may be replaced with the cyano group by Sandmeyer's method, i.e., by heating a solution of the compound with cuprous sodium or potassium cyanide:¹⁹³



The reaction is carried out in nearly neutral medium, since in a medium of high pH unreactive diazotates are formed. A nearly neutral condition may be maintained by the addition of sodium bicarbonate or lime. It is also necessary to hold low the concentrations of the diazo compound and the metallic cyanide during the reaction. The reaction is usually carried out below 50°, though in some instances the reaction proceeds at a good rate at 10°. This method has been employed for the preparation of nitrated and chlorinated benzonitriles,¹⁹⁴ cyano-naphthalenes,¹⁹⁵ sulfonated cyanonaphthalenes,¹⁹⁶ and cyanopyridines.¹⁹⁷

As an example of the procedure the preparation of 4-chloro-5-nitro-2-cyanotoluene is here described: To one-fourth of the solution of the diazonium compound prepared from 339 gm of 4-chloro-5-nitro-2-aminotoluene maintained at 30° is added a mixture of 450 gm sodium cuprous cyanide dissolved in 700 cc water, 1000 gm ice, 110 gm lime; then 26 gm sodium cyanide are introduced and the second, third, and fourth quarter portions of the diazo solution are added, after each portion adding 26 gm of sodium cyanide. The precipitate is then filtered, washed free of lime and dried. The yield is 75% of the theoretical.³²⁹

The diazo group may be replaced also with a cyano group by heating the diazo compound in aqueous solution with an alkali metal cyanide in the presence of finely divided metallic copper.¹⁹⁸

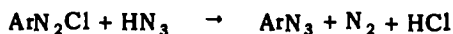
The diazo group may be replaced with the *thiocyano* group by heating the diazo compound in aqueous solution with potassium thiocyanate and cuprous thiocyanate.¹⁹⁹ The diazo group may be replaced with the *isocyano* group by heating the diazo compound with potassium cyanate and copper powder.²⁰⁰ Phenyl isocyanate has been obtained in low yield by this method.

The *sulfonic* group may be made to replace the diazo group by passing sulfur dioxide into a solution of the diazonium sulfate, and subsequently heating the solution with copper powder. Replacement with the sulfonic group may be effected also by adding an alcoholic solution of sulfur dioxide and sodium bisulfite to the solution of the aromatic diazonium sulfate and subsequently decomposing the product with copper powder.²⁰¹

The diazo group may be replaced with the *nitro* group by adding freshly precipitated cuprous oxide to a solution of diazonium nitrite containing an excess of nitrous acid.²⁰² Red cupro cupric sulfite has also been used as a catalyst in this reaction.²⁰³ Cupro cupric sulfate is best prepared by adding an equivalent of sulfite to an aqueous solution of copper sulfate. Another satisfactory method is to add a solution of a mixture in equimolecular quantities of copper

sulfate and sodium nitrate to the diazo compound. Ortho and para dinitrobenzenes have been prepared by this method, but a diazo group in ortho position to a halogen remains unaffected.²⁹⁹ Replacement of the diazo group with the nitro group can be brought about by the action of copper powder on the double compound of the diazonium nitrate and mercuric nitrite.²⁰⁴ The decomposition of diazonium cobaltinitrites with an aqueous solution of sodium nitrite in the presence of cuprous oxide and cupric sulfate results in the replacement of the diazo group with the nitro group.²⁰⁵

Diazo compounds are converted readily to aryl azides by reaction with hydrazoic acid:²⁰⁶



This reaction fails only when the azide formed is unstable in cold, weakly acid solution. The reaction is applicable to diazo compounds of naphthalene and its derivatives. Azides may be formed from diazonium compounds by the prolonged action of *p*-toluenesulfonamide and caustic (*Dutt-Wormall reaction*). Phenyl azide has been obtained in 75% yield by this method from benzenediazonium chloride.³⁰⁰ Aryl azides *explode* in contact with concentrated sulfuric acid; they are converted to aminophenols with 50% sulfuric acid.²⁰⁷

Replacement of the Diazo Group with Aromatic Radicals

Diazo compounds, when subjected to the proper reducing conditions, may be converted in part to diaryls:



Copper and zinc dust have been employed as the reducing agent.²⁰⁸ The yields are generally low in this reaction. Improved yields have been obtained by carrying out the reaction in acetic anhydride, using copper powder as the reducing agent.²⁰⁹

Ammoniacal cuprous oxide converts aromatic diazo compounds containing negative substituents to diaryls. The reaction has been applied to diazo compounds with nitro, cyano, aldehydo, carboxyl and sulfonic groups.²¹⁰ Diazo compounds devoid of negative substituents are converted to azo compounds by the treatment. The cuprous oxide is prepared by reducing a cupric salt with hydroxylamine.²¹¹ This method has been of special service for the preparation of compounds of the naphthalene series.²¹²

The tendency to give diaryl derivatives is quite pronounced with nitro aromatic diazonium compounds, and such compounds may yield a high proportion of diaryls under the normal conditions employed for the replacement of the diazo group with a halogen atom.²¹³

Dry diazonium chlorides react with benzene or other aromatic compounds in the presence of aluminum chloride to form diphenyl derivatives.²¹⁴ Chlorinated compounds are formed as a by-product due to the replacement of the diazo group with chlorine. Pyridine and quinoline react with phenyldiazonium chlor-

ide in the absence of aluminum chloride to form phenylpyridine and phenylquinoline respectively.

Aqueous solutions of diazo compounds brought near the neutral point by the addition of acetate, combine directly with benzoquinone, naphthoquinones and quinone oximes.²¹⁵ The quinone is usually dissolved in alcohol or acetic acid, and the diazo compound is added with stirring. Nitrogen is given off and the reaction is complete at room temperature within twenty-four hours.

Diazonium salts and *n*-diazotates react with quinones of the benzene and naphthalene series in alcoholic or acetic acid solution with the formation of arylquinones often in good yield.³¹⁰ Nitrosoacylanilides have been used in the reaction with success.³¹¹ Copper powder and cuprous chloride have been used as catalysts.³¹²

The Gomberg Reaction

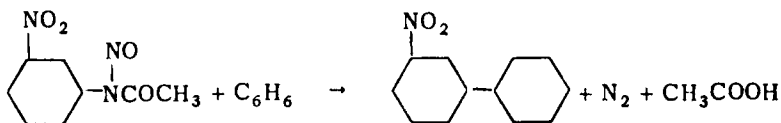
Conditions which cause the formation of free aromatic radicals from diazo compounds may bring about the formation of diaryls through the reaction of such radicals with aromatic compounds.²¹⁶

Acylated diazonium compounds decompose on heating, giving rise to free aromatic radicals which combine to form a diaryl. If the decomposition is effected in the presence of an aromatic compound, this may combine with the free radical giving rise to a mixed diaryl.²¹⁷ Aromatic radicals may be generated from alkaline diazotates, and advantage has been taken of this fact in the Gomberg method of preparation of diaryls.²¹⁸

The amine is diazotized in the smallest possible quantity of water, the solution of the diazo salt is mixed with the desired aromatic compound, and the mixture is introduced drop by drop into cold concentrated aqueous caustic with good agitation. The organic layer is separated after completion of the reaction, and the diaryl is isolated by fractional distillation.

The yields of diaryls obtained by the Gomberg reaction are generally not satisfactory. The use of sodium acetate in place of caustic results in an improvement in yields in some instances, as in the preparation of nitrodiphenyls from nitroanilines and benzene.²¹⁹ The Gomberg reaction has been employed for the preparation of fluorenones from substituted anthranilic esters.²²⁰ The method is not the best available for bringing about the union of aromatic Radicals with pyridine.²²¹

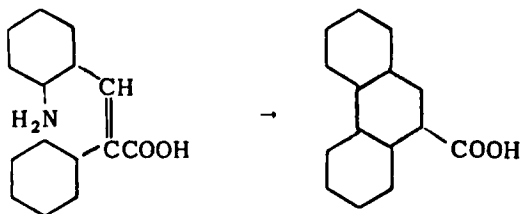
The reaction of nitrosoacylanilides with aromatic compounds, which presumably proceeds by way of the formation of an aromatic radical,³¹³



is related to the Gomberg reaction. It provides an important route to diaryls, tertiary and quaternary phenyls and other complex derivatives.

*The Pschorr Synthesis*²²²

The diazo group in an aromatic compound may be removed to be replaced with an aromatic group in a side chain attached to the aromatic nucleus of the diazo compound. The reaction results in the formation of a new ring, and takes place most readily when it results in the appearance of a stable molecular structure. Thus, the diazo compound derived from *o*-aminobenzylidenephénylacetic acid, heated with copper powder gives 9-phenanthrenecarboxylic acid:^(*)



The reaction is carried out in the following manner: Twelve parts of the amino-benzylidenecarboxylic acid are suspended in 160 parts of water, 120 parts of concentrated sulfuric acid are added, followed by a solution of 4 parts of sodium nitrite in 20 parts of water. The solution of the diazo compound formed is then filtered, and 14 parts of copper paste are added. The mixture is stirred until a test drop no longer produces a coloration with naphthylamine. The precipitate of phenanthrene carboxylic acid is purified first by dissolving in aqueous ammonia and precipitating with dilute acid, and finally by crystallization from acetic acid. The yield is about 93% of the theoretical.

Cyclization can occur only when the two aryl groups of the α -arylcinnamic acid are on the same side of the double bond. Solvents used for the reaction include water, methanol, ethanol and dioxane; of these, water is the most commonly used. Diazotization has been effected by use of sodium- or potassium nitrite and hydrochloric acid, as well as with alkyl nitrites; the latter have given consistently better yields.

Cyclization proceeds at 50° in many instances; occasionally higher temperatures are required. Cyclization has been effected in certain cases in hot alkaline medium. Sodium hypophosphite, NaH₂PO₂, in dioxane or alcohol has been employed as a cyclizing agent. The most satisfactory conditions will have to be determined experimentally for every particular case.

A phenolic compound may be formed by a side reaction as a result of the replacement of the diazo group with hydroxyl. Phenol formation becomes pronounced in the preparation of polycyclic compounds with more than three rings, and of phenanthrene derivatives bearing groups that exert a hindering effect to the cyclization reaction. Phenol formation occasionally takes place when a

(*)Pschorr's work involved the synthesis of the diazo compound from an aryl acetic acid and *o*-nitrobenzaldehyde in three steps; namely, a Perkin condensation of the aldehyde with the aryl acetic salt, reduction of the resulting nitro body with an ammoniacal ferrous sulfate solution, and the final diazotization of the resulting amino compound. The requisite diazo compounds have been prepared by this series of reactions by subsequent investigators.

strong electronegative group is attached to the α -phenyl group of the aminophenylcinnamic acid. Phenol formation has been greatly reduced or entirely eliminated in some cases by diazotizing the amine in ethanolic hydrogen chloride solution with amyl nitrite, and then bringing about cyclization with copper powder. Still better results have been obtained when cyclization was induced with sodium hypophosphite in dioxane. Cleavage of acetoxy or benzoxy groups are other side reactions that may occur under special conditions.

Substituents in the α -phenyl group attached to the ethylenic system have little or no effect on the course of the cyclization reaction. The preparation of phenanthrene derivatives with substituents at both 4 and 5 positions is difficult or impossible in some instances. Interference is less marked by alkoxy groups. Anomalous examples are known however of 4- and 5- substituted phenanthrene derivatives forming in exceptionally high yield.

Decarboxylation of the acid formed in the Pschorr synthesis has been effected in early days by dry distillation under reduced pressure, a process which has been improved subsequently by the addition of copper bronze. The preferred procedure at present is to heat the compound in quinoline or quinaldine in the presence of copper powder, or of a copper salt. Phenanthrene carboxylic acids with substituents at 1,2,3, or 4-positions appear to undergo decarboxylation quite readily, and those with alkoxy groups at any position with difficulty. Halogenated derivatives are also decarboxylated with difficulty and give poor yields of the corresponding halophenanthrenes.

Phenanthrene may be obtained by the Pschorr reaction from *as*-*o*-aminostilbene by treating an alcoholic solution of the diazo compound derived from this amine with sodium hypophosphite solution and a trace of copper.²²³ Phenanthrene may be obtained also in 80% yield by heating *cis*-*o*-diazostilbene sulfate with sodium hyposulfite and copper powder. The presence of the carboxyl group in aminobenzylidenephylacetic acid causes the stabilization of the *cis*-isomeride and thus favors ring formation from the diazo compound.

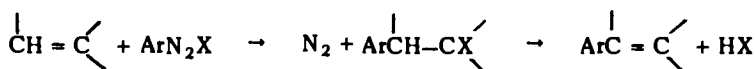
The Pschorr synthesis has been applied to the preparation of many types of polynuclear aromatic hydrocarbons.³³¹ 1-Naphthyl-*o*-aminocinnamic acid, subjected to the reaction, affords chrysene-7-carboxylic acid, and 2-methyl-*o*-aminocinnamic acid gives 1,2-benzanthracene-4-carboxylic and 4,3-benzphenanthrene-1-carboxylic acids. Di- α -*o*-aminobenzlidene-*m*-phenylenediacetic acid gives 1,2,7,8-dibenzanthracene-4,5-dicarboxylic acid in low yield.²²⁴ The method has been employed for the preparation of phenanthrene N-methyltetrahydropapaverine from N-methyltetrahydropapaverine,²²⁵ and aporphin from 1-*o*-aminobenzyl-2-methyltetrahydroquinoline.²²⁶ The isoquinoline ring in these examples exerts a stabilizing effect, favoring the spatial configuration required for the Pschorr reaction.

Fluorene is obtained, together with *o*-hydroxyphenylmethane, when diphenylmethane-*o*-diazonium sulfate is boiled in aqueous solution.²²⁷ Fluorenones are formed similarly from diazo compounds derived from some substituted *o*-aminobenzophenones.²²⁸ These are representative of a process of ring closure which can occur whenever a diazo group is ortho to the methylene or ketone group in

a diarylmethane or a diarylketone.²²⁹ Other polynuclear hydrocarbons that have been prepared by the Pschorr synthesis include 1,2-benzanthracene, 3,4-benzophenanthrene, 1,2,5,6-dibenzanthracene, 3,4,5,6-dibenzophenanthrene, 1,2,3,4-dibenzophenanthrene, and cholanthrene.

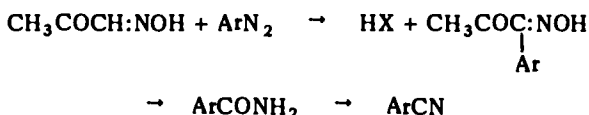
Arylation of Unsaturated and Oximino Compounds

Diazonium compounds and nitrosoacetanilides are capable of reacting with certain unsaturated bodies in the presence of cupric chloride or sulfate, replacing a hydrogen atom attached to an ethylenic carbon with an aromatic group (*Meerwein reaction*):



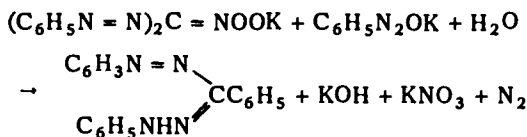
The reaction proceeds well with compounds having activated or polarized ethylenic bonds, such as coumarin, cinnamic and crotonic acids, cinnamylidene acetic ester and dienes.³¹⁴ The diazonium salt may be generated in situ from a triazene.³¹⁵

A hydrogen atom attached to the carbon atom of an oximino group may be replaced with an aromatic group by reaction with an aromatic diazo compound. Oximino compounds react only in the presence of a cupric catalyst, while nitroparaffins and nitroformazans react in the absence of a catalyst. Arylated derivatives obtained from oximino compounds have served as starting points of many other syntheses, viz. of aldehydes, ketones, acids, amides, and nitriles.³¹⁶ Benzamides and benzonitriles have been prepared, for example, from the oxime $\text{CH}_3\text{COCH:NOH}$:



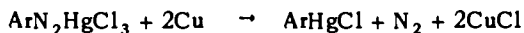
One and two equivalents of n-benzene diazotate give mono- and diarylnitromethane by reaction with nitromethane in alkaline solution; benzeneazodiphenylnitromethane, $C_6H_5N=NC(C_6H_5)_2NO_2$, is obtained as the end product with three equivalents of n-benzenediazotate.³⁷

Benzenediazotate reacts with nitroformazan with oxidative replacement of the nitro group with a phenyl group:³¹⁸



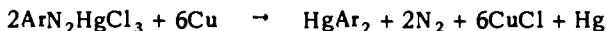
Replacement of the Diazo Group with Metals

The diazo group may be replaced with certain metals by subjecting the double compounds of aromatic diazo compounds with the halides of these metals to the action of copper powder or certain other reducing agents:²³⁰



The method has been applied most successfully to the preparation of aryl mercury compounds. Copper is found to be quite satisfactory as the reducing agent for the purpose, although stannous chloride gives fairly satisfactory results. The reaction is carried out in a non-ionizing solvent, such as acetone or ethyl acetate.

The double salts of mercuric chloride with diazo compounds having positive substituents, which are of the type $\text{ArN}_2\text{HgCl}_3$, undergo the reaction most readily and, depending on the proportion of copper used, they yield arylmercuric chlorides, according to the reaction already shown, or a diaryl according to the equation:²³¹



When the aryl radical in the diazo compound contains negative groups, the double salts formed are of the type $(\text{ArN}_2)_2\text{HgCl}_4$, and when these are subjected to the action of copper powder under the usual conditions, they yield chiefly haloaryl derivatives and hydrocarbons. The aryl mercury compound may be prepared from these complexes by adding them with vigorous agitation to a suspension of three atomic equivalents of copper powder in acetone cooled to -10 to -20° .²³²

Replacement of the diazo group with *tin* may be effected by subjecting the stannic chloride double salt of the diazo compound to the action of finely divided copper, zinc, or tin. Best results are obtained when tin is used as the reducing agent:²³³



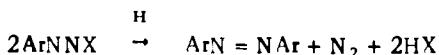
The reaction proceeds energetically and with evolution of heat. It may be carried out by adding the powdered double salt to a suspension of the metallic powder in ethyl acetate at such a rate as to maintain the liquid at the boiling temperature.

It is of interest to note that both metallic mercury and tin are attacked directly by benzenediazonium chloride, mercury giving phenylmercury chloride, tin, diphenylstannic chloride.²³⁴

The *lead* double salts $\text{C}_6\text{H}_5\text{N}_2\text{PbCl}_6$ and $\text{C}_6\text{H}_5\text{N}_2\text{PbCl}_3$, reduced by copper or zinc powder in boiling acetone or other suitable solvent, give only a small yield of triphenyllead chloride, $(\text{C}_6\text{H}_5)_3\text{PbCl}$, and diphenyllead dichloride, $(\text{C}_6\text{H}_5)_2\text{PbCl}_2$.²³⁵

Azo Compounds Through the Decomposition of Diazo Bodies

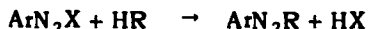
Diazo bodies may be decomposed under the action of mild reducing agents such as cuprous salts, with loss of two nitrogen atoms and the formation of an azo compound:³¹⁹



When a mixture of unlike diazonium compounds is subjected to the action of the reducing agent, two symmetrical azo compounds are formed with only traces of an unsymmetrical azo compound, unless one of the diazonium salts carries a negative substituent, in which case an appreciable proportion of the unsymmetrical azo compound may be formed.³²⁰

COUPLING REACTIONS

Aromatic diazo compounds are capable of reacting with aromatic bodies to form azo compounds:



The nitrogen atoms forming the azo group are both trivalent. The reaction, which is bimolecular, is one of condensation between the undissociated, polarized diazo compound and the aromatic body in an activated state, in which a hydrogen atom has acquired an induced positive charge.²³⁶ The process is referred to as *coupling*. The most important factor affecting the reaction is the pH of the medium in which it is carried out. Coupling takes place most readily and completely at about the neutral point, although the stability of the diazo compound also drops to a low value at this point. Negative substituents enhance the coupling power of the diazo compound and the reaction can take place in increasingly acid solution with increase in the number of such substituents in the aromatic nucleus of the diazo compound. The ease of reaction of diazo compounds with various substituents increases in the order *p*-OCH₃, *p*-CH₃, H, *p*-Cl, *p*-SO₃H, *m*-NO₂, *p*-NO₂. Highly nitrated aromatic diazo compounds are capable of coupling in strongly acid solution. Ortho and meta tetrazo compounds are also capable of coupling in acid solution.²³⁷ The optimum pH value for maximum reactivity of various substituted aromatic compounds are as follows: ethers 13, alkyl substituted 12, unsubstituted 11, sulfonated and halogenated 8, mononitrated 5, dinitrated 2. Aryl or alkylamino groups in the para position decrease the coupling power of the diazo compound, also enhancing their light sensitivity. The reaction is usually carried out in aqueous solution. The optimum conditions for coupling depend both on the nature of the diazo compound and of the coupling component.

Phenols are coupled in alkaline solution. A solution of the compound in aqueous sodium carbonate is used, if the phenol is soluble in aqueous carbonate; otherwise the phenol is dissolved in the minimum amount of aqueous caustic, and the calculated quantity of sodium carbonate is added to neutralize the acid generated in the course of the reaction. It is desirable to employ sufficient carbonate for the formation of sodium bicarbonate at the end of the reaction. The solution of the diazo compound is added slowly with stirring to the chilled solution of the phenolate. Coupling occurs readily.

Coupling with ortho and para nitrodiazo compounds cannot be carried out in alkaline solution, since these bodies undergo molecular rearrangement under the action of alkalis, or even of sodium carbonate, to non-coupling isodiazotates. Coupling with such compounds may be carried out in the presence of sodium acetate, and in certain special cases, in the presence of calcium carbonate or magnesia. Similar procedures are em-

ployed when dealing with diazo compounds in which ortho substituents are liable to be replaced with hydroxyl groups under the action of alkalis. Coupling may often be successfully effected in such cases by avoiding the use of any excess of alkali in dissolving the coupling component and carrying out the reaction at as low temperatures as possible. Pyridine has been used successfully as the acid-fixing agent in these reactions. Couplings with very sensitive compounds, such as 2,4-dinitrodiazobenzene, should be carried out in acid solution at a low temperature.

Phenols may be coupled by adding aqueous solutions of the diazo compound to the phenol in acetic acid in the presence of sodium acetate.

Amines are coupled as a rule in weakly acid or neutral solution. The procedure is varied depending on the stability of the amine. Amines that are difficultly soluble in water are dissolved in dilute acids, if solution is possible, and the diazo compound is then added. Sodium acetate or carbonate may be added to the reaction mixture if coupling proceeds slowly, but it is essential to keep the liquid acid to Congo Red. Successive additions of acetate or carbonate may be made, keeping the acidity at this point. It is desirable to neutralize the liquid fully toward the end in order to force the reaction to completion. If the amine tends to form a diazoamino compound, coupling should be carried out in as strongly acid solution as possible. The addition of alcohol, or other water-miscible liquid may aid the reaction if coupling proceeds slowly.

Amines which do not dissolve in water or dilute acids, such as diphenylamine and phenylnaphthylamine, are most satisfactorily coupled in solution in an organic liquid. Methyl and ethyl alcohols, acetone and pyridine may be employed for the purpose. In industrial practice, such amines are coupled by emulsifying them in water by use of a soap as an emulsifying agent, and subjecting them to the action of the diazo compound. Coupling may also be accomplished by solubilizing the amine by sulfonation. Sulfonated amines are dissolved in water as their alkali metal salts, and sodium acetate equivalent in amount to the free acid present in the diazo solution and that formed in the coupling reaction is added; then the diazo solution is introduced with stirring. Coupling reactions with diazo compounds having several negative substituents and aromatic amines have been carried out in methanol solution.²³⁸

The end point of the reaction is determined by placing a drop of the reaction mixture on a filter paper and touching the colorless ring surrounding the central pigmented spot with a drop of a solution of a reactive phenolic compound, such as the sodium salt of β -naphthol, R-salt, or resorcinol, then with a drop of a solution of sodium carbonate or dilute caustic. If unreacted diazo compound is present, the formation of a dye is observed in this test. If no colorless ring appears at the fringe of the moist circle produced by the original drop, because of the solubility of the azo compound, a small portion of the reaction mixture is "decolorized" by saturating it with sodium chloride to precipitate the azo compound. The test is then carried out with a drop of the colorless liquid. The presence of unreacted coupling component may be determined in a similar manner by using a solution of a reactive diazo compound, instead of the sodium phenolate.

Soluble azo compounds may be readily analyzed by titration with titanium trichloride, and the method is employed for the determination of yield.²³⁹

Alkaline couplings of hydroxy compounds generally take place quite rapidly, but coupling of amino compounds in acid solution takes place less readily, as a rule, and requires from a few minutes to several hours.

On the industrial scale it is not always necessary to employ sufficient solvent to dissolve both reactants completely; it is desirable however that at least one reactant be completely in solution. The other reactant should be present in the form of a finely precipitated solid. For monazo colors, the volume of solvent is 3 to 6 liters per gram mole of the compound, although much greater volumes are also often used, especially in the last couplings of polyazo colors.

The stable *diazosulfonates* do not couple with phenols or amines even when warmed in alkaline solution. They may be converted to the labile form by mixing the dry salt with dry bromide-bromate mixture and powdered sodium acid sulfate and dissolving the mixture in water.²⁴⁰

sym-Azo compounds have been obtained in high yield from diazo compounds of the naphthalene series by adding an acid solution of the sulfate of the diazonium compound to freshly precipitated cuprous oxide suspended in water.²⁴¹ This transformation also takes place on treating *diazosulfonates* of the naphthalene series with sodium sulfite.²⁴² *asym-m*-Xylidine and *p*-cumidine yield symmetrical azo compounds under the action of ammoniacal cuprous oxide.²⁴³

Coupling can be accelerated by warming, or by increasing the alkalinity, although the decomposition reaction is also favored by a rise in temperature and increase in alkalinity. Coupling may also be accelerated by increasing the concentration of the reactants, and by adding water binding agents. Slow coupling bodies generally give best yields when the reaction is carried out in the cold, and near the neutral point. In cases where coupling is slow, a great improvement in yields may result when the reaction is carried out in a mixture of water and pyridine.²⁴⁴ Quinoline also has a beneficial effect.

It would appear that in the reaction with phenols, it is the free phenol formed by the dissociation of the phenolate that couples with the diazo compound. High alkalinity may retard or prevent coupling by depressing the dissociation of the phenolate, and by causing the formation of an alkaline isodiazotate. In general, weakly acidic phenols couple satisfactorily over a wide range of pH, and strongly acidic phenols over a narrow range. Difficulty may be experienced in coupling a strongly acidic phenol with a diazo compound, such as diazoxylene, which needs fully alkaline conditions for coupling. 2-Hydroxy-1,4-naphthoquinone cannot be coupled successfully in alkaline medium.

When the coupling compound contains both a hydroxyl and an amino group, the course of the reaction varies according to whether coupling is effected in acid or in alkaline solution. Thus, γ -aminonaphtholsulfonic acid, coupled with diazotized benzidine in acid solution, gives Diamine Violet, while coupling in alkaline solution leads to the formation of Diamine Black. If coupling is first carried out in acid solution, it may be possible to introduce a second azo group by carrying out the coupling reaction in alkaline solution. The reverse order of coupling has not been successfully carried out.

It has been pointed out that the coupling ability of diazo compounds is enhanced by negative groups attached to the aromatic nucleus and that reactivity increases with increase in the number of negative groups in the nucleus. 2,4-Dinitrodiazobenzene and 2,4,6-trinitrodiazobenzene couple readily with β -naphthol in a mixture of 1 part concentrated sulfuric acid and 2 parts concentrated phosphoric acid. Tetrazo compounds also are capable of coupling in acid solution. The coupling ability of diazo compounds derived from various amines ranges, in order of increasing activity, as follows: aniline, 3,4,6-trichloroaniline, 3,5-dinitroaniline, *p*-nitroaniline, 2,6-dichloro-4-nitroaniline, 2,4-dinitroaniline and 2,4,6-trinitroaniline.²⁴⁵

The amount of nitrite employed in the preparation of the diazo compound must not exceed the theoretical, if the coupling reaction is to be carried out in acid solution or if, after coupling, the solution is to be acidified in order to isolate the azo compound. A small excess of nitrite is without effect if the reaction is carried out in alkaline solution.

More than one arylazo group may enter the nucleus of the coupling component in the course of the coupling reaction. A bis- and trisazo compound may be obtained from phenol by using a sufficient excess of the diazo compound, and progressively increasing the alkalinity of the reaction mixture.²⁴⁶ The formation of bisazo compounds is favored as the concentration of the reactants in the solution is increased. Alkyl groups in the nucleus, particularly if present in the meta position to a hydroxyl group, favor the formation of bisazo compounds. *m*-Dihydric phenols give bis- and even trisazo compounds with comparative ease. 1,5-Dihydroxynaphthalene gives a monoazo compound, while 1,6-dihydroxynaphthalene may yield a bis-, or even a trisazo compound. Multiple coupling may be avoided with compounds that normally tend to give bis- or trisazo compounds, by adding the diazo solution slowly and with good agitation. The reaction with dihydroxy compounds is often carried out in weakly acid solution in order to avoid the formation of the bisazo compounds.

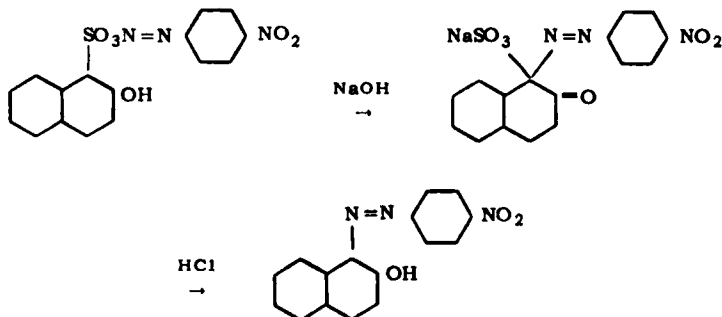
Coupling may take place in some cases with elimination of groups present in the coupling component. This occurs, for example, with highly reactive azo compounds when they are made to react with β -naphthol or with 2,3-hydroxynaphthoic arylamides having a halogen, methylene, or sulfonic acid group in the α -position. These groups are ejected from the nucleus and replaced by the arylazo group. N-Alkyl-2-methylenedihydroquinolines and N-alkyl-2-methylene-trialkylindolines lose the alkyl group attached to the ring nitrogen atom on coupling.

In the reaction of a primary aromatic amine with a diazo compound in weakly acid solution, a mixture of two azo compounds may be obtained due to an exchange of the diazo group and a subsequent two fold coupling.²⁴⁷ This is explained by assuming that an equilibrium exists in solution between the diazo salt, amine and nitrous acid, the free nitrous acid causing the diazotization of the amine in the coupling component. An exchange of a diazo group with an arylazo group already present in the molecule may also take place.²⁴⁸ The ability of a diazo compound to replace an arylazo group depends on its relative reactivity. The exchange takes place more readily in the naphthalene series.

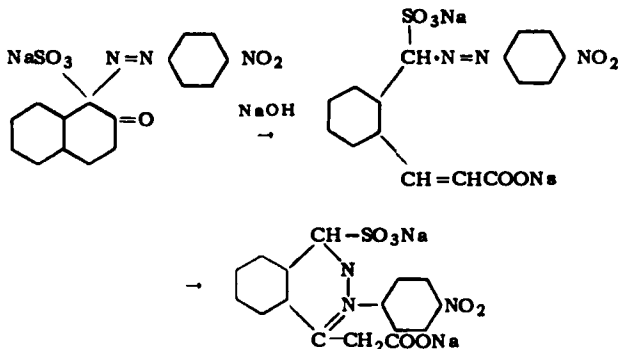
In some instances the normal coupling reaction fails to occur and another reaction takes place. α -Diazopyridine fails to couple normally with phenol, but reacts to give a mixture of α -(*o*'-hydroxyphenyl)pyridine and α -(*p*'-hydroxyphenyl)pyridine.²⁴⁹ Pure *p*-nitrodiazobenzenediazonium sulfate, reacting in alcoholic solution with *o*- and *p*-propenylphenol gives the *p*-nitrophenylhydrazone of *o*- and *p*-hydroxybenzaldehyde.²⁵⁰ A similar reaction is also observed with anethole, isoapirole, isosafrole and isoeugenol.²⁵¹

A quantitative yield of *p*-nitrobenzeneazo- β -naphthol (Para red) is obtained when a

solution of 4'-nitrobenzene-2-naphthol-1-diazosulfonate in a molecular equivalent of aqueous sodium hydroxide is acidified:



Acidification of the solution of the sodium salt of the diazosulfonate in an excess of aqueous sodium hydroxide, on the other hand, results in the formation of 3-(4'-nitrophenyl)-1,3-dihydronaphthalazine-4-carboxylic acid 1-sulfonic acid, in the form of its sodium salt:²⁵²



The sulfonic acid in this compound may be replaced with a hydroxyl group by hydrolysis with hydrochloric acid. When the resulting compound is boiled with dilute mineral acids, it is converted to 4-nitro-3-phenylphthalaz-1-one, while, if it is treated with cold potassium dichromate, it is decarboxylated to 4-nitro-3-phenyl-4-methylphthalaz-1-one.

Diazo compounds other than diazonium salts including diazotates, diazo sulfonates, diazo cyanides, diazo ethers and diazo esters, are capable of undergoing the coupling reaction.

Effect of Substituents on Coupling Ability

Homologs of benzene having a structure resembling that of mesitylene are alone capable of coupling with diazo compounds of strong coupling power, such as 2,4,6-trinitrodiazobenzene.²⁵³ Crystalline azo derivatives have been obtained from cyclopentadione, indene, mesitylene, isodurene, 1,2,3,5-tetramethylethyl- and pentamethylbenzene, and 3,4-benzpyrene.

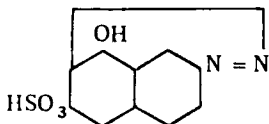
Phenols, as a rule, couple quite readily with diazo compounds. Negative sub-

stituents in the phenolic compound retard the coupling reaction; this is in contrast to the activating influence of such substituents, if present in the aromatic nucleus of the diazo compounds. Chlorine exerts a more powerful deactivating influence than bromine, while iodine slightly activates the phenolic compound. Positive substituents cause an increase in the activity of phenolic compounds. A second hydroxyl group in the meta position has a strong activating effect. Thus, resorcinol undergoes coupling readily over a wider range of pH and with a greater variety of diazo compounds than phenol.²⁵⁴ Catechol is capable of undergoing the coupling reaction under the proper conditions,²⁵⁵ and quinol may be made to couple with diazo compounds by benzoylating one hydroxyl group, or converting the phenol into its sulfuric ester. A methoxyl group in phenols exerts a powerful activating influence, particularly if present in the meta position. An amino group in the meta position in phenol also causes an increase in coupling power. Phenols containing nitro groups react with diazo compounds to form diazoxy compounds. Picric acid, for example, gives with diazobenzene the compound $C_6H_5N = NOC_6H_2(NO_2)_3$.

Dihydric aromatic phenols, as well as aromatic diamines and amino phenols in which two hydroxyl or amino groups, or the amino and the hydroxyl groups are in *ortho* or *para* position to each other, are oxidized to quinones by diazo compounds and cannot, therefore, be coupled under the normal coupling conditions. Smooth coupling may be effected, however, when thiosulfates or thiocyanates are added to the reaction mixture.

Monohydric phenolic ethers are incapable of coupling under normal conditions with most diazo compounds; they couple only with highly reactive diazo compounds, such as 2,4-dinitrodiazobenzene.²⁵⁶ Ethers of dihydric phenols, such as those of resorcinol or phloroglucinol, dissolved in glacial acetic acid, slowly couple with the more reactive diazo compounds, such as *p*-nitrodiazobenzene. Phloroglucinol ethers are capable of coupling with diazobenzene.²⁵⁷ 9-Methyl-anthranol methyl ether couples with *p*-nitrodiazobenzene at the 9-position with loss of the methyl group. Coupling of phenols is occasionally accompanied with partial or complete removal of the alkyl group of the ether.²⁵⁸

Naphthols undergo the coupling reaction more readily than phenol, α -naphthol more readily than β -naphthol. The latter yields a mono azo compound, while the former is capable of forming a bisazo compound. A dihydric naphthol or an amino naphthol in which the hydroxyl or amino groups are attached to different rings are more reactive than monohydric naphthols. An internal coupling may be brought about in the case of some aminonaphthols by treating the diazo compound with alkalis. For example, the diazo compound from 2,8-aminonaphthol-6-sulfonic acid gives



The coupling power of some of the more common phenolic compounds, in de-

scending order of activity range as follows: phloroglucinol, α -naphthol, resorcinol, β -naphthol, catechol, salicylic acid.²⁵⁹

Aromatic amines are capable of undergoing reaction with diazo compounds, although they show a lower order of activity than phenols. Only the more active diazo bodies yield azo compounds with aniline. The presence of alkyl or alkoxyl groups in the nucleus of aromatic amines in the ortho and more particularly the meta position facilitates coupling. Especially good coupling is observed with amines having such substituents in both an ortho and meta position. *p*-Xylidine, cresidine, *m*-toluidine, 2,5-dimethoxy- and diethoxyanilines and 2-chloro-5-methoxyaniline are capable of giving amino azo compounds with diazo salts. Substitution of hydrogen atoms attached to nitrogen with aryl or alkyl groups also enhances the coupling power of aromatic amines.²⁶⁰ Thus, dimethylaniline readily gives dimethylamino azo compounds. The presence of an ortho substituent in tertiary aromatic amines prevents coupling. Diphenyl-*p*-phenylenediamine fails to undergo the coupling reaction.

The formaldehyde bisulfite compound, $\text{HOCH}_2\text{SO}_3\text{Na}$, reacts with amines to form methyl- ω -sulfonates, $\text{RNHCH}_2\text{SO}_3\text{Na}$. These compounds readily couple with diazo salts to form amino azo compounds. The methyl- ω -sulfonate group may be readily removed by hydrolysis after the coupling operation.

m-Diamines also possess strong coupling power. Di-*para*-substituted *m*-diamines couple with some difficulty. Monochloro- and mononitro-*m*-phenylenediamine undergo the coupling reaction readily. *m*-Diamines with one or two substituents couple readily regardless of whether the amino groups are primary or are alkylated. *N*-Alkylation of di-*p*-substituted diamines causes a reduction in the coupling power; the symmetrical and asymmetrical dimethyl compounds yield mixtures of azo compounds and triazens. *o*-Coupling may be sterically hindered by substituents in the amino group.³⁰⁴ Complete alkylation suppresses the coupling reaction.⁹⁰ Only nitro diazo compounds are capable of coupling with 1,3-diamino-4,6-dihalobenzenes.

Acylation of primary arylamines usually suppresses the coupling power, *p*-Toluenesulfonamides of α - and β -naphthylamine and the internal sulfonamide 1,8-naphthasulfam are capable of coupling with *p*-nitrodiazobenzene.²⁶² β -Anthramine undergoes the coupling reaction, but amines of the anthraquinone series do not couple. Arylcyanamides undergo the coupling reaction.²⁶³

Among amino naphthols and their sulfonic acids, some, such as 2-amino-1-naphthol-4-sulfonic acid and 1-amino-3,6-disulfonic acid fail to couple at all. Others, like 1,2-aminonaphthol and its 6-sulfonic acid couple under special conditions to form monoazo compounds, or like 1,8-aminonaphthol-4- and -5-sulfonic acids couple to give a mixture of mono- and bisazo compounds. There are others, finally, which couple under the usual conditions.

The coupling position of the azo group in the reaction of diazobenzene with monoamino quinolines, with the amino group at 3, 5, 6, 7 and 8 position are 4, 8 and 6, 5, 8 and 5 respectively.

Pyrrole, indole and other similar heterocyclic ring compounds are capable of undergoing the coupling reaction.

Position of Attachment of the Azo Group

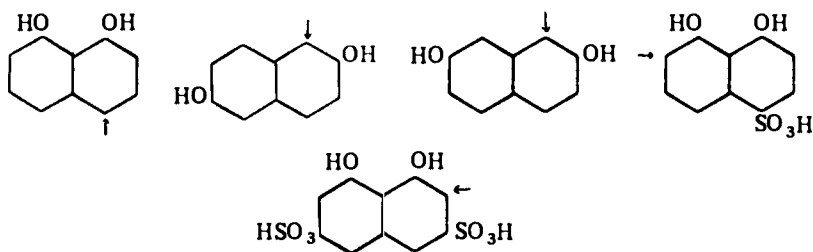
The diazo group preferably attaches itself at the *para* position in a coupling reaction, although a small amount of *ortho* compound is also formed.²⁶⁴ If the *para* position is occupied, then the *ortho* position is the preferred point of attack. If the reaction results in the formation of a bisazo compound, then, one azo group enters the *para* position, one the *ortho*. The azo group may enter the *ortho* position in exceptional cases if this position is activated by substituents. Phenolic compounds in which a carbonyl or sulfonic group is present in the *para* position couple with diazo compounds with removal of these groups, giving *p*-hydroxyazo compounds. Resorcilic acid, i.e., 2,4-dihydroxybenzoic acid, gives a mixture of a 2,4-dihydroxyazo- and 2,4-dihydroxy-5-carboxydiazo compound.

α -Naphthol and its derivatives couple at position 2 and 4. Strong couplers generally first attack position 4, while weak couplers preferentially attack position 2. If position 4 is substituted, coupling occurs exclusively at position 2; if both the 2 and 4 positions are occupied, then coupling fails to take place. A sulfo group in 3 or 5 position greatly diminishes the reactivity of position 4, and coupling takes place exclusively at position 2, although, strongly coupling compounds give a mixture of 2- and 4-azo compounds.

The compounds with the azo group at position 4 are soluble in dilute caustic, while those with the azo group at position 2 are sparingly soluble in caustic.

β -Naphthol couples at the adjacent α -position. If this position is occupied with a substituent, then, either coupling does not take place at all, or the substituent is replaced by the azo group. The presence of a sulfo group in position 8 retards or prevents the reaction.

The position of attack of various dihydroxynaphthalenes is indicated below by arrows:



The behavior of naphthylamines in coupling reactions parallels that of the corresponding naphthols, the directing influence of the amino group being comparable with that of the hydroxyl group. α -Naphthylamine couples in the 4-position, though with the more reactive diazo compounds some coupling in the 2-position may also take place.³⁰⁵ α -Naphthyl-N-sulfamic acid, $C_{10}H_7NHSO_3H$, couples exclusively in position 4; diazo-*o*-anisidine couples at position 4 with α -naphthylnitramic acid, $C_{10}H_7NHNO_3$.

Naphthalene derivatives in which an amino and a hydroxyl group are attached

to the naphthalene ring, the amino group determines the point of attack in acid solution, and the hydroxyl group in alkaline solution.²⁶⁵

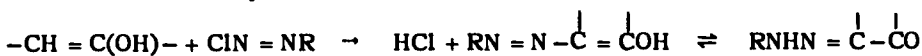
6-Hydroxyhydrindene couples at position 4; 5-methyl-6-hydroxyhydrindene fails to couple, but 4-methyl-6-hydroxyhydrindene forms a 5-azo compound.²⁶⁶

Coupling with Reactive Methylene

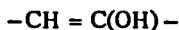
The great reactivity of the diazo group comes to evidence in the reaction of diazo compounds with "activated" methylene. Notable among the class of compounds with reactive methylene groups are the carbonyl compounds RCH_2COR' , in which R is a negative residue, such as carboxyl, carbonyl, cyano, etc. These compounds generally show strong keto-enol tautomerism:



The azo group apparently first replaces the hydrogen atom attached to the carbon atom in the enolic form of the compound, forming azo compounds which are tautomeric with hydrazones:



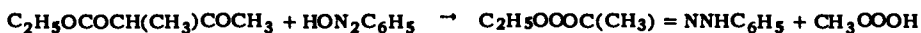
Coupling with the enolic compound is interesting in that the grouping



characterizing the enol is present also in phenols.

Among substances of this type capable of coupling with diazo compounds are malonic ester, acetylacetone, glutaric acid and its esters, acetonedicarboxylic acid, acetonesulfonic acid, ω -nitroacetophenone, acetophenone- ω -sulfonic acid, lignocellulose, cyclic ketones, pyrazolones.²⁶⁷ Heterocyclic systems, including pyrroles, indoles, 2-thiophenamines,³²¹ α -picoline, quinaldine,³²² and indazole are also capable of coupling with diazo compounds.

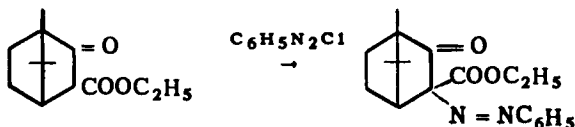
Free acetoacetic acid couples with benzenediazonium hydroxide with loss of carbon dioxide to form the phenylhydrazone of pyruvaldehyde, $CH_3COCH = NNHC_6H_5$.²⁶⁸ Ethyl methylacetoacetate loses the elements of acetic acid on coupling with benzenediazonium hydroxide, giving the phenylhydrazone of pyruvic ester:



Carboxyl groups are often removed during the coupling reaction, if they are attached to the carbon atom with which the diazo group unites. Acetonedicarboxylic acid loses both carboxyl groups to give bisbenzeneazoacetone (mesoxalic phenylhydrazone), as does also chelidonic acid, this compound yielding bisbenzeneazopyrone on reaction with diazobenzene.

Hydrazones formed through the reaction of cyclic β -keto esters are unstable in aqueous alkalis, the latter causing the rupture of the ring, with the formation of the hydrazone of a keto dicarboxylic acid.²⁶⁹ The anilides of cyclic keto esters are stable toward alkalis.

Benzenediazonium chloride adds to ethyl 3-camphorcarboxylate in aqueous alcoholic solution in the presence of sodium ethoxide and sodium acetate, forming ethyl 3-phenylazo-3-camphorcarboxylate in 88 to 97% yield.³⁰¹



α -Ketohomocamphoric acid phenylhydrazone is formed when this compound is refluxed for six hours with aqueous-alcoholic caustic.

Pyrazolones are formed by ring closure from the azo compounds obtained by coupling a diazo body with compounds $\text{RR}'\text{CHCH}_2\text{COOR}''$, in which R and R' are a carbalkoxy, carboxamide, cyanido, or keto groups, and R'' is an alkyl group. Ring closure proceeds spontaneously on carrying out the coupling in alcohol, R and R' being ejected in the process, and the elements of an alcohol being eliminated.²⁷⁰

Nitro paraffins couple with diazo compounds, in weakly alkaline solution, as a rule; the diazo group unites with the carbon atom to which the nitro group is attached with formation of hydrazones and arylation with loss of diazo nitrogen.²⁷¹ Nitromethane yields a number of compounds with diazobenzene.²⁷² Dinitromethane couples with two molecular equivalents of diazobenzene to form bisbenzeneazodinitromethane. Other nitro paraffins, including secondary nitro paraffins, react with one molecular equivalent of the diazo compound, although 2,4,6-trichloro- and -tribromobenzenes yield bisazo compounds with nitroethane.²⁷³

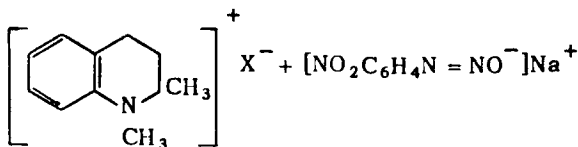
Butadiene and its homologs react with strongly coupling diazo compounds.

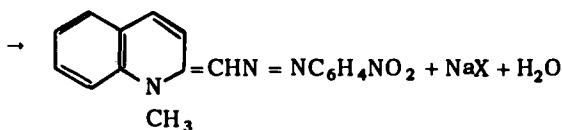
Butadiene, isoprene, α -methylbutadiene, and β,γ -dimethylbutadiene undergo the coupling reaction with *p*-nitrodiazobenzene and 2,4-dinitrodiazobenzene.²⁷⁴ The reaction proceeds best in acetic acid solution, or in alcohol, and most readily with β,γ -dimethylbutadiene. Unstable hydrazo compounds are obtained when the azo compounds are reduced. β -Phenylbutadiene undergoes the coupling reaction, while its dimer does not; 2,3-diphenylbutadiene also couples, and α,α -diarylethylenes couple if the aromatic group contains certain negative substituents.²⁷⁵

Styrenes couple with difficulty with the more reactive diazonium compounds. Phenyl- and *p*-methoxyphenylacetylenes couple at the β -atom, hydration occurring simultaneously with the formation of a ketohydrazone:³²³



Positively substituted diarylethylenes $\text{Ar}_2\text{C} = \text{CH}_2$ couple with diazo compounds to arylaminoazomethine carbonium salts $[\text{Ar}_2\text{CCH} = \text{NNHAr}]^+\text{X}^-$. Methylcarbonium salts in hot aqueous solution, mixed with an antidiastote couple to a methylene azo compound:³²⁴

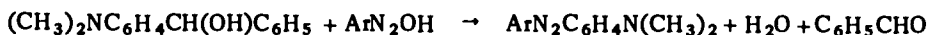
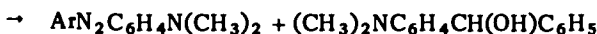
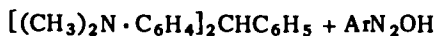




Diazo coupling also takes place with *aliphatic diazo* compounds with elimination of arylhydrazide chlorides and the aliphatic diazo nitrogen:³²⁵

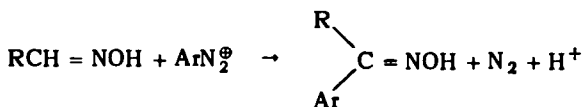


Diazo compounds attack alkylated aminodi- and -triphenylmethanes, giving an aldehyde and a dialkyl aminoazo compound:²⁷⁶

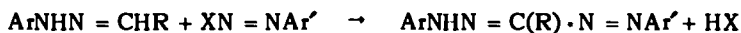


p-Nitrodiazobenzene in alcoholic suspension removes the hydrocarbon side chain from *p*-dimethylaminopropenylbenzene, *p*-(CH₃)₂NC₆H₄·CH=CHCH₃, giving 4-nitro-4'-dimethylaminoazobenzene.

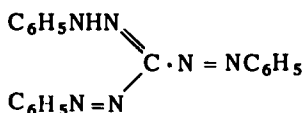
Aldoximes may be arylated by aromatic diazo compounds in the presence of copper:³³⁰



Many *hydrazones* react with diazo compounds to form azo hydrazones, the so-called *formazyls*:²⁷⁷

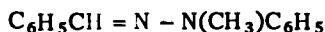


Hydrazones resulting from the reaction of diazo bodies with compounds containing a reactive methylene often readily react with a second molecule of the diazo compound to form formazyls. Malonic acid reacts with three molecular equivalents of diazobenzene, first forming the formylhydrazone of mesoxalic acid, then formazyl carboxylic acid, and finally formazylazobenzene,²⁷⁸



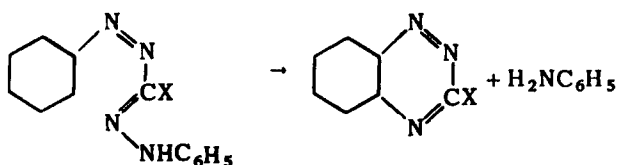
Glutaconic acid, treated with two equivalents of diazobenzene, gives β-(N,N'-diphenylformazyl)acrylic acid, C₆H₅NHN=C(N=NC₆H₅)CH=CHCOOH. Di-formazyls result from compounds containing the grouping -CO·CH₂CH₂CO-, when these are subjected to the action of excess diazohydroxide.

Hydrazones of *as*-secondary arylhydrazines, such as



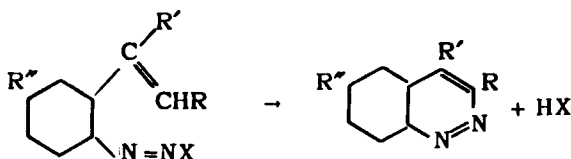
cannot couple with diazo compounds; on the other hand, benzaldehyde phenylhydrazone couples to form phenylformazyl, C₆H₅NHN=C(C₆H₅)·N=NC₆H₅.²⁷⁹

Formazyls may be converted to phentriazines under the action of mineral acids:



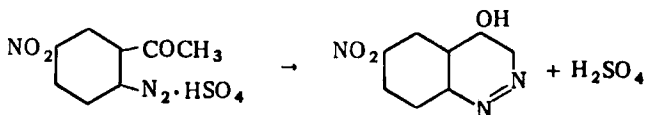
Formation of Cinnolines; Widman-Stoermer Reaction

A diazonium group in *ortho* position to an ethylene side chain in an aromatic compound may couple with the β -carbon atom in the side chain, forming a six-membered ring, a cinnoline:



The reaction takes place spontaneously, as a rule, if substituents in the side chain induce a strong electron donating power in the β -carbon atom. Reaction fails to take place if R' is hydrogen, carboxyl, and R is an aryl group; reaction proceeds readily if R' is an aryl group, even if R is also an aromatic residue. Both the *cis* and *trans* forms of the diazo compound are capable of forming cinnolines. This transformation, giving rise to cinnolines from *o*-ethylenic amines, is the basis of the Widman-Stoermer reaction.²⁸⁰ The Pschorr reaction is a competitor of this reaction, if R is an aromatic group, and α -phenyl- α -aminophenyl- β -1-naphthylethylene gives on diazotization, either a cinnoline or a 2-phenylchrysene, depending on the conditions:

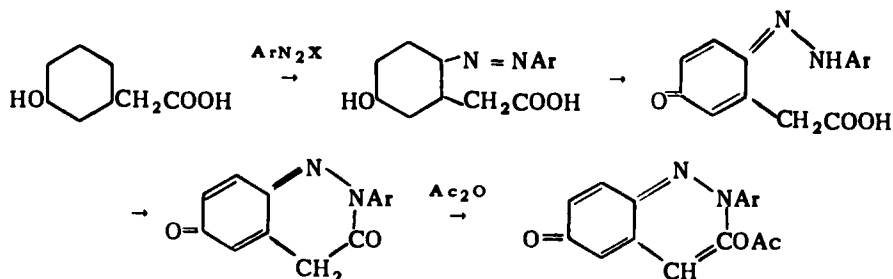
4-Hydroxycinnolines are formed on diazotization of certain *o*-aminoaryl ketones:²⁸¹



The yields are high when a negative group is present in the *ortho* or *para* position with respect to the diazo group. When this condition is not satisfied, the yields are of the order of 10%, and the main product is a phenolic compound.

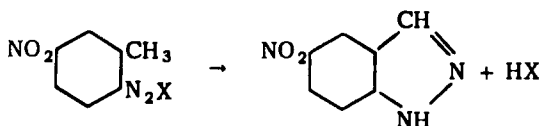
Diazotization of *o*-aminopropiolic acids, followed by boiling of the diazo compound in aqueous solution, results in the formation of 4-hydroxy-3-carboxycinnolines. This is known as the *Richter reaction*.²⁸² The process apparently involves an intramolecular coordination of the diazonium cation and the cationoid carbon atom, and the subsequent addition of the hydroxyl ion, the proton which is eliminated as HX being derived from the solvent. The carboxyl group of the cinnoline may be readily removed by heating at 260° .

Tetrahydrocinnolines are formed when azo compounds resulting from the coupling of diazo compounds with *m*-hydroxyphenylacetic acid are warmed with acetic anhydride:²⁸³



Formation of Indazoles

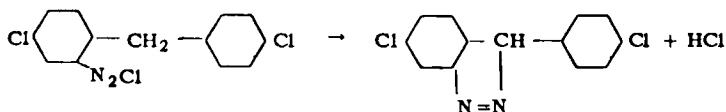
Indazoles, or 4,5-benzpyrazoles, are formed through the coupling of a diazo group with a methyl group in the *ortho* position in an aromatic compound:²⁸⁴



The mechanism of the reaction is the same as that of the Widman-Stoermer reaction, and the same activating influences are operative in the two reactions. A nitro group in the *meta* or *para* position with respect to the methyl group favors the formation of the indazole, while a second methyl group in the *meta* position hinders the reaction. The best conditions for the formation of indazole must be determined for each particular case.

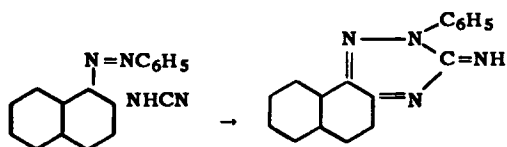
In the anthraquinones series, a diazo group attached to a carbon atom adjacent to one bearing an alkyl chain, can couple with the α -carbon atom of the alkyl group to form an indazole, coupling being accomplished by heating an aqueous solution of the diazonium hydroxide.²⁸⁵

The methylene group in diphenylmethane, although incapable of reaction with external diazo compounds, couples with an *ortho* diazo group in the molecule, forming an indazole:²⁸⁶

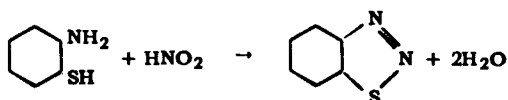


Formation of other Nitrogen Ring Compounds

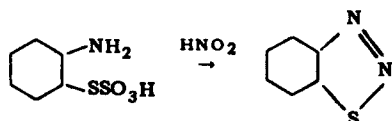
The azo compound obtained by coupling β -naphthylcyanamide with diazobenzene undergoes internal condensation forming β -naphthaphenyliminoketotriazine:²⁸⁷



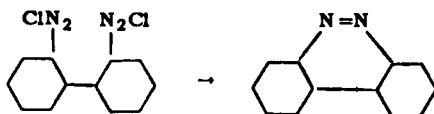
Diazo compounds derived from *o*-aminothiophenols undergo internal condensation immediately upon their formation, giving *thiodiazoles*:²⁸⁸



So strong is the tendency toward the formation of the thiodiazole that *o*-aminothiosulfuric acids, when diazotized, are converted to the thiodiazole with ejection of the sulfonic group:²⁸⁹

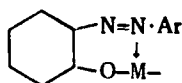


Diphenylene azones are obtained when a solution of diphenyl-*o,o'*-diazoo salt is run into a cold acid solution of cuprous chloride or cuprous bromide:²⁹⁰



Formation of Metallic Complexes

Aromatic azo compounds with a hydroxyl group in an aromatic nucleus in an *ortho* position with respect to the diazo group form complexes with certain metallic salts.²⁹¹ These are chelated compounds which may be properly represented as



The geometrical arrangement of the aromatic group in the chelate molecule is *trans*. Compounds of chromium and copper yield such metallic complexes. They play an important role in the dye industry. The complexes are known as metallic lakes.⁶⁵

Crystalline complexes have been obtained through the combination of antimony trichloride with diazonium salts containing groups of basic character.²⁶¹

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CHAPTER 28

AROMATIC HALOGEN COMPOUNDS

Halogens react with aromatic compounds with varying ease. Fluorine reacts so energetically that it is generally impossible to control the reaction so as to obtain fluorine substitution products of the original aromatic compound without deep-seated decomposition. Of the other halogens, chlorine reacts most vigorously, and iodine least readily. The reactivity of bromine is quite marked, and many of the methods of preparation of chlorinated and brominated compounds present close parallelisms. Halogenation, i.e., replacement of a hydrogen atom in an organic compound with a halogen, may be effected by the direct action of halogens upon the compound or by use of halogenating agents. The latter are halo compounds that readily yield their halogen in part or in whole.

AROMATIC CHLORINE COMPOUNDS

Methods of Chlorination

Chlorination with Elemental Chlorine

Aromatic compounds may be readily chlorinated by the action of chlorine. The rate of reaction and the type of chlorinated compound formed are influenced by the temperature, radiation, and the catalytic agent, if one is present. Chlorination may be carried out by conducting gaseous chlorine into the compound or through its solution in a suitable solvent. The chlorine may also be introduced in the form of a solution in a suitable solvent. The degree of chlorination varies according to the concentration of the halogen in the reaction mixture.

A dilute solution of chlorine in glacial acetic acid is especially suitable for the chlorination of amines and phenols, which are easily over-halogenated or oxidized. In order to maintain a more or less constant low chlorine concentration in the solution, an *N*-chloroanilide is employed to which a little hydrochloric acid is added initially. Chlorine is formed by the reaction of hydrochloric acid with the chloroanilide:



Since hydrogen chloride is regenerated through the chlorination of the aromatic body, its concentration, and therefore that of the chlorine, remains more or less constant. Suitable chloroanilides are 2,4-dichloroanilide, chloroamine, and *N*-chloro-*p*-nitroacetanilide. The procedure is to dissolve molecular equivalents of the chloroanilide and the compound to be chlorinated in acetic acid, to add 1/100 to 1/20 molar equivalent of hydrochloric acid in the form of the constant boiling aqueous solution, and to allow the mixture to stand at 15° in the dark until all the available chlorine is utilized.

In the chlorination of homologs of benzene, the halogen may enter the nucleus or may attack the side-chain, depending on the conditions. Nuclear chlorination takes place if the reaction is conducted in the dark. Higher temperatures and radiation favor chlorination of the side-chain. Phosphorus trichloride and sulfur also promote side-chain substitution,¹ while ferric chloride and many other catalysts favor substitution of the nucleus. *tert*-Butyl benzene and *o*-butyltoluene show an exceptional behavior, and are chlorinated in the nucleus in the sunlight.

It is of interest to note that when gaseous chlorine is subjected to the action of light it becomes activated, and is then capable of attacking the side-chain in homologs of benzene.² The halogen may be activated also by the electric arc or by electric discharge.³ On activation by the latter method the gas undergoes some contraction in volume.

Ether, alcohol, chloroform, and glacial acetic acid are the solvents commonly employed in conducting chlorination reactions.⁴ Other solvents employed for the purpose are carbon tetrachloride, tetrachloroethane, nitrobenzene, phosphorus oxychloride, sulfuric acid, and water. The use of sulfuric acid is of advantage in the chlorination of aromatic amines.

The influence of catalysts in chlorination reactions is very marked. The catalysts usually employed are ferric chloride, metallic iron, iodine,⁵ aluminum-mercury couple, sulfur, and antimony monochloride.⁶ Antimony trichloride, molybdenum pentachloride,⁷ zinc chloride, and tin have also been used. Phosphorus pentachloride,⁸ like phosphorus trichloride and iodine, promotes side-chain chlorination. The catalytic action of iodine and sulfur apparently depends upon the intermediate formation of a chlorine compound, iodine forming iodine monochloride and sulfur, sulfur tetrachloride. The catalytic activity of antimony trichloride is apparently due to the intermediate formation of antimony pentachloride. It is probable that halogenation involves attack by positive halogen, and that the role of the catalysts is to promote its formation.

Anhydrous ferric chloride, which is the most effective chlorine carrier, may be obtained in satisfactory condition for use by heating the commercial product under reduced pressure, while passing dry chlorine or hydrogen chloride over it until the material begins to sublime. The product thus treated is cooled and kept out of contact with moisture. The presence of moisture in the catalyst may cause side reactions. Small amounts of the anhydrous product, generally about 1%, effectively catalyze the chlorination reaction. Use of the minimum required quantity makes possible the purification of the final product by distillation with little difficulty.

Chlorination with Nascent Chlorine

Occasionally it is of advantage to carry out the chlorination of a hydrocarbon with nascent chlorine. The reaction proceeds more vigorously than with elemental chlorine, and it is possible to use the exact required amount of the chlorinating agent. The compound to be chlorinated is dissolved or suspended in hydrochloric acid, and a suitable oxidizing agent is added. Satisfactory oxidizing agents are alkali chlorates,⁹ manganese dioxide, potassium permanganate,¹¹ potassium dichromate, and hydrogen peroxide.

In the *Raschig method* of chlorination of benzene,¹⁰ which is carried out in the vapor phase, air acts as the oxidizing agent in the presence of cupric chloride or a mixture of cupric and ferric chlorides at 180°.

Chlorination by Use of Chlorinating Agents

Substitution of hydrogen atoms in organic bodies with chlorine may be brought about by use of various chlorinating agents. Their use may present advantages over the use of chlorine. Compounds usually employed as chlorinating agents include chlorine compounds of sulfur, such as sulfuryl chloride, thionyl chloride, chlorosulfonic acid, sulfonic chlorides; chlorine compounds of phosphorus, such as phosphorus pentachloride; antimony pentachloride, etc.

Chlorination with Chlorine Compounds of Sulfur

The usual procedure followed in carrying out a chlorination with *sulfuryl chloride*, SO_2Cl_2 , is to distill this compound onto the substance to be chlorinated and to allow the mixture to stand for some time. If the reaction proceeds slowly at ordinary temperature, the mixture is heated. This compound is useful as a mild chlorinating agent for phenols.

The chlorinating action of sulfuryl chloride may be markedly enhanced by various catalysts. Sulfuryl chloride containing a little sulfur chloride reacts vigorously with benzene in the presence of aluminum chloride.¹¹ Substitution in the ring or in the side-chain is promoted, depending on the nature of the catalyst. Chlorides of antimony, iron, molybdenum, and aluminum favor nuclear substitution, whereas the chlorides of phosphorus, and to a lesser extent, the chlorides of manganese, arsenic, and bromine promote substitution in the side-chain. Sulfur promotes both types of substitution.¹²

Thionyl chloride, SOCl_2 , may be employed as a chlorinating agent to a limited extent; it fails to react with benzene even at 200°, but certain benzene derivatives are chlorinated by this reagent. Azobenzene, for example, is converted to 4,4'-dichlorobenzene at 180–200°; toluene yields benzal chloride and benzotrichloride at 230–250°. Naphthalene is converted to 1,4-dichloronaphthalene when heated at 230–250° with thionyl chloride. This reagent may serve for the replacement of sulfonic and nitro groups with chlorine. Replacement of sulfonic groups proceeds when the sulfonic acid or its chloride is heated with thionyl chloride in a sealed tube at 160–180°.¹³

Chlorosulfonic acid is known to exert a chlorinating action under certain circumstances. Anthraquinone, for example, is transformed to the chloride of dichloroanthracene disulfonic acid on treatment with this reagent.¹⁴

Chlorination with Other Agents

Chlorination of aromatic compounds may be effected by use of *phosphorus pentachloride*. When this compound is made to react with homologs of benzene, the hydrogen atoms in the side-chain are first replaced, before substitution of any nuclear hydrogen takes place.¹⁵ *Ortho* and *para* xylenes, heated with phosphorus pentachloride in a sealed tube at 200°, are converted to penta- and hexa-

chloroxylenes, $\text{Cl}_3\text{CC}_6\text{H}_4\text{CHCl}_2$ and $\text{Cl}_3\text{CC}_6\text{H}_4\text{CCl}_3$. Helianthron, refluxed for half an hour with a mixture of phosphorus oxychloride and phosphorus pentachloride, is converted to 4,5,8,4',5',8'-hexachlorohelianthron.¹⁶

Antimony pentachloride has been used for the chlorination of high molecular aromatic compounds, especially ketones. Chlorination with this reagent may be effected at a lower temperature by using iodine as a catalyst. Perchlorinated compounds generally result, which often undergo ring cleavage with the formation of perchlorinated acids. Hexachlorobenzene may be the ultimate product of the reaction.¹⁷

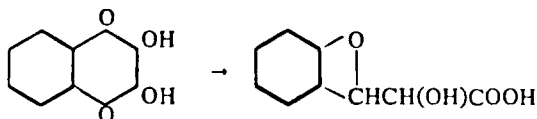
Sodium hypochlorite may be employed for the chlorination of phenolic compounds in alkaline solution.

When salicylic acid, dissolved in an equivalent of cold aqueous alkali, is treated with a molecular proportion of sodium hypochlorite, it is converted to mono- and dichlorosalicylic acids.¹⁸

The reagent has been employed for the chlorination of hydroxy- and methoxybiphenyl.¹⁹

Chlorination of 4-hydroxybiphenyl has been carried out by slowly adding one molecular equivalent of hypochlorite solution to a cooled solution of one mole of the phenol in six liters of water containing a molal equivalent of caustic, allowing the mixture to stand for an hour, and finally warming to 40°. After filtration and cooling, the 3-chloro-4-hydroxybiphenyl formed is precipitated by the addition of hydrochloric acid.

α -Naphthol in alkaline solution, treated with sodium hypochlorite, is converted to 2-chloro-1-naphthol.²⁰ Dihydroxy- α -naphthoquinone is converted to the lactone of α -phenylglycerine carboxylic acid when heated with hypochlorous acid.²¹



Sodium hypochlorite has been employed for the chlorination of the side-chain in aromatic compounds.

† Benzyl chloride is obtained, for example, from toluene by adding the hydrocarbon with good agitation, to an aqueous solution of one-third equivalent of sodium hypochlorite cooled to -5°, then adding a half molal equivalent of sulfuric acid very slowly, in the course of a few hours. Benzyl chloride is formed in 60 to 70% yield, and may be recovered by fractional distillation.

Mono- and dichlorotoluenes are also converted to the corresponding chlorobenzyl chlorides, the dichloro compound reacting more slowly than the monochloro compound. More highly chlorinated toluenes fail to react. When xylenes are subjected to the action of sodium hypochlorite, the first product is m -methylbenzyl chloride, and this probably offers the best method of preparation of the compound. On further chlorination, the halogen attaches itself to the methyl group with which the first halogen atom is combined.

Chlorination of aromatic compounds with aqua regia generally results in the formation of chloranil. Phenol is very readily attacked by this reagent.²²

Chlorination by Replacement of Other Groups or Elements

The sulfonic group in certain aromatic compounds is replaceable with chlorine. Anthraquinone-1-sulfonic acid and halo-, nitro-, and hydroxyanthraquinone sulfonic acids, for example, exchange their sulfo group for a chlorine atom in the presence of water. Thus, alizarin sulfonic acid, treated with chlorine, gives 3-chloroalizarin.²³ Potassium anthraquinone- α -sulfonate in aqueous solution containing hydrochloric acid gives with chlorine at 100° α -chloroanthraquinone. The β -sulfonic compound similarly gives the β -chloro compound. Anthracene-1,8-disulfonic acid, heated with a mixture of hydrochloric acid and an alkali metal chlorate, is converted to 1,8-dichloroanthraquinone.²⁴

When 2-chloro-1-toluene-4-sulfochloride is heated at 150–200° and chlorine is conducted through the melt until no more hydrogen chloride is evolved, the side-chain is fully chlorinated, and at the same time, the sulfochloride group is replaced with chlorine.²⁵

Tetrachloro-o-benzoquinone is obtained when pyrocatechol sulfonic acid is chlorinated in glacial acetic acid.²⁶

The sulfonic group in anthraquinone-1-sulfonic acid or its salts may be replaced with chlorine by treatment with thionyl chloride at elevated temperatures.²⁷ The corresponding dichloro compounds are obtained from 1,5- and 1,8-disulfonic chlorides. Anthraquinone- β -sulfonic acid gives the chloro compound in low yield, but yields may be greatly improved when the sulfonic acid group is first converted to the sulfonic chloride, and this is heated at an elevated temperature with thionyl chloride.²⁸ Replacement may also be effected with nascent chlorine.

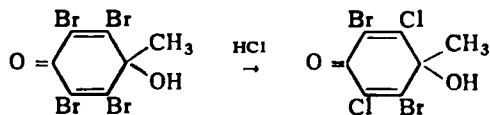
The nitro group in α -nitroanthraquinone and its derivatives may be replaced with chlorine by direct halogenation in the proper solvent. If aliphatic side-chains are attached to the anthraquinone nucleus, these are chlorinated. The method has been applied to β -nitro- and α,β -polynitroanthraquinones and their derivatives.²⁹

2,7-Dinitrofluorenone has been converted to 2,7,9,9-tetrachlorofluorene by heating the compound at 180° with phosphorus pentachloride.³⁰ Thionyl chloride would appear to be better suited for the replacement of nitro groups with chlorine.

The hydroxyl group in certain substituted phenols is readily replaceable with chlorine by treatment with *p*-toluenesulfonic chloride, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, in the appropriate solvent. 1,4-Dichloro-2,6-dinitrobenzene is obtained by this method from 4-chloro-2,6-dinitrophenol when the reaction is carried out in diethylaniline. If the reaction of this phenol with *p*-toluenesulfonic chloride is carried out in aqueous sodium carbonate solution, the sulfonic ester of the phenol is obtained.³¹ The hydroxyl group in *p*-hydroxyquinoline is replaced with chlorine when the compound is heated with phosphorus pentachloride to 110 to 115°.³²

Bromine in certain aromatic compounds may be interchanged for chlorine by treatment with this element. Bromine in bromobenzene is exchangeable in this manner.³³ Iodobenzene, however, does not undergo this exchange reaction, but adds two atoms of chlorine forming phenyl iodochloride. An exchange of bro-

mine atoms for chlorine takes place also when 2,3,5,6-tetrabromomethylquinol is treated with alcoholic hydrochloric acid, with the formation of 2,5-dibromo-3,6-dichloromethylquinol:³⁴



The *amino* group in aromatic amines may be replaced with chlorine indirectly by diazotization followed by treatment with hydrochloric acid in the presence of copper powder or cuprous chloride. The subject has been dealt with in the chapter on aromatic diazo compounds. The reaction of chlorine with α -amino-anthraquinone in acetic acid solution gives nitrogen-free polychloro compounds.

Formation of Nuclearily Chlorinated Compounds through Intramolecular Rearrangement

Aromatic N-chloroacylamines undergo molecular rearrangement under the action of hydrogen chloride giving rise to nuclearily chlorinated acylated bases:³⁵



The reaction proceeds via the intermediate formation of molecular chlorine through the reaction of the chloramine with hydrogen chloride.

This fact is utilized in the preparation of a solution of chlorine of known concentration in acetic acid solution, preferably using for the purpose aliphatic chloramines, or an aromatic chloramine with depressed nuclear reactivity, such as Chloramine T or N-chloro-2,4-dichloroacetanilide.

The reaction proceeds much less readily when chlorine atoms or nitro groups are present in the nucleus. The presence of a nitro group in *ortho* position to the arylamino group prevents the reaction.³⁶

Chlorinated aromatic compounds may also be prepared, of course, by various coupling reactions. They may be obtained, for example, by use of the Grignard reaction. Thus, chloroethylbenzene, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{Cl}$, has been obtained from the chloroethyl ester of toluene-*p*-sulfonic acid, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{OCH}_2\text{CH}_2\text{Cl}$, and phenylmagnesium bromide.³⁷ Chlorinated aromatic ketones may be obtained through the reaction of acyl chlorides with certain chlorinated aromatic compounds in the presence of aluminum chloride. The general process of chloromethylation offers an effective method for the preparation of benzyl chloride, naphthylmethyl chloride, their derivatives and other aromatic chloromethylated compounds.

Chlorination of Various Types of Compounds

Chlorination of Benzene and its Homologs

Benzene is readily chlorinated by passing the halogen in the gaseous form into the liquid in the presence of a catalyst. Finely divided iron, or iron chlo-

ride are satisfactory catalysts. These catalysts gain in activity as the reaction progresses.³⁸ Other substances which act as catalysts are iodine, aluminum chloride, aluminum-mercury couple, and antimony chloride.³⁹ An alternative procedure is to pass chlorine into benzene until the liquid is saturated with the gas, and then to trickle the solution down a well-cooled tower containing scrap iron. Reaction sets in at once, with evolution of hydrogen chloride and formation of monochlorobenzene, together with a little dichlorobenzene, the compounds forming 30% and 2% of the mixture respectively. In the chlorination of benzene a certain amount of the di- and polysubstituted compounds are always formed together with monochlorobenzene.

In order to obtain the monochloro compound as the principal product, it is necessary to pass an amount of chlorine considerably less than that required for the formation of monochlorobenzene, and the chlorination should be carried out in the cold. When 60% of the theoretically required quantity of chlorine is used, less than 60% of the benzene is converted to chlorinated compounds, and of this amount about 10% is in the form of the dichlorobenzenes, principally the *para* compound, with a little of the *ortho* isomer. It is claimed that the formation of di- and polychlorinated products is minimized if the iron catalyst is fully covered with benzene, and the halogen is led over the surface of the liquid.⁴⁰ Hexachlorobenzene is formed when 10% of iron chloride is added to benzene and chlorine is passed through the liquid until no further adsorption takes place.

While benzene is chlorinated by substitution in the dark and in the presence of catalysts, addition of the halogen takes place when the liquid is illuminated during chlorination, and catalysts are absent. Addition also takes place when benzene is chlorinated at its boiling point and under illumination. The final product obtained under these conditions consists of a mixture of isomeric 1,2,3,4,5,6-hexachlorohexanes.⁴¹

Benzene may be effectively chlorinated with *sulfuryl chloride* in the presence of aluminum chloride or other catalysts, such as iodine, thionyl chloride, sulfur, and sulfur monochloride. Chlorination takes place very readily in the presence of aluminum chloride if the sulfuryl chloride contains a little sulfur monochloride. Varying degrees of chlorination may be achieved by regulating the amount of chlorinating agent used; in this way, di-, tri-, tetra-, penta- and hexachlorobenzenes have been obtained.¹¹

Homologs of benzene may be nuclearly chlorinated in the same manner as benzene, i.e., in the presence of a catalyst such as ferric chloride.⁴² They undergo halogenation more readily than benzene itself. Toluene gives a mixture of *o*- and *p*-chlorotoluenes when an amount of the halogen less than that required for mono chlorination is employed. These isomers cannot be separated by physical methods. A progressively greater degree of halogenation leads to the formation of 2,3- and 2,4-dichlorotoluenes, 2,3,4- and 2,4,5-trichlorotoluenes, and finally tetrachloro- and pentachlorotoluenes.

Tetrachlorotoluene is obtained in nearly quantitative yield when toluene is treated with chlorine in the presence of iron or anhydrous ferric chloride, first at 5–12° until the formation of trichlorotoluene is complete, then at a gradually rising temperature so as to maintain the mass in a fluid condition, until a temperature of 50° is reached.⁴³

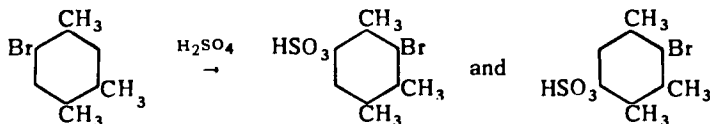
Ortho-chlorotoluene may be obtained in the pure form by chlorinating sodium *p*-toluene-

sulfonate in aqueous solution at 10 to 15°, and hydrolyzing the *o*-chlorotoluene-*p*-sulfonate which separates out in the form of colorless crystals.⁴⁴ Hydrolysis is effected by means of sulfuric acid and superheated steam.

Para-chlorotoluene is obtained similarly from sodium *o*-toluene sulfonate. The chlorination is carried out at 0–5°. The 4- and 6-chloro sulfonic acids are formed simultaneously in this reaction, but they may be readily separated by taking advantage of the difference of their solubility in water. When a solution of one gram mole of sulfonic acid in 650 to 700 cc of water is used, the 6-chloro compound precipitates out directly from the reaction mixture. The 4-chloro-*o*-sulfonic acid is precipitated out upon further concentration of the solution.⁴⁵

Cleavage of the side-chain often takes place when one attempts to prepare highly chlorinated derivatives of homologs of benzene.⁴⁶

Transfer of substituents often occurs when aluminum chloride⁴⁷ or concentrated sulfuric acid⁴⁸ are made to act upon halogen derivatives of benzene and its homologs. For example, when monobromobenzene is heated with aluminum chloride above 100°, benzene and dibromobenzene are formed. Cold, fuming sulfuric acid of low sulfur trioxide content converts bromopseudocumene into the sulfonic acid of isomeric bromopseudocumenes:



Chlorination of the Side-Chain in Homologs of Benzene⁴⁹

Substitution of hydrogen atoms in the side-chain occurs when the chlorination of toluene and other homologs of benzene is carried out at higher temperatures or under illumination in the absence of catalysts. Side-chain chlorination occurs almost exclusively when vapors of toluene are chlorinated under the action of ultraviolet rays.

Chlorination under illumination with mercury lamps is effected in a glass tower packed with glass rings. Mercury lamps are placed in the tower spaced 4 feet apart. Toluene heated to 80 to 100° is introduced at a controlled rate at the top of the tower, and dry chlorine is admitted at the bottom. The temperature is maintained at 111°, i.e. just below the boiling point of toluene, by regulating the rate of introduction of reactants.

In the preparation of benzyl chloride, C₆H₅CH₂Cl, from toluene, the usual procedure is to heat toluene to its boiling point and to pass the halogen through the liquid until the theoretical amount of chlorine is absorbed. The chloride may be purified by fractional distillation.

The necessity for carrying out the reaction in an acid proof vessel may be obviated by adding an excess of sodium carbonate and keeping the liquid well agitated.⁵⁰

It is possible to replace more than one atom of hydrogen in the methyl group by chlorine.

The side-chain in certain derivatives of toluene may be chlorinated by treating the compound with the halogen at 120–140° in an autoclave. Toluene-*p*-sulfonic acid is converted quantitatively to benzyl chloride *p*-sulfonic acid by this method.⁵¹

The methyl group in toluene-*p*-sulfonic acid may also be chlorinated by passing chlorine through a suspension of the sodium salt of the sulfonic acid in boiling carbon tetrachloride until the theoretical amount of chlorine is absorbed.⁵²

The more complex the alkylated compound, the more difficult becomes the chlorination of the alkyl group. *Cresols* and similar compounds cannot be chlorinated directly in the side-chain. It is necessary to protect the hydroxyl group in such compounds; this is generally accomplished by converting the phenols to their carbonic, phosphoric, or *p*-toluenesulfonic esters.

The carbonate of *o*-cresol, fused at 80° or dissolved in carbon tetrachloride at 25–30° and treated with chlorine, while illuminated with a mercury vapor lamp, gives first the carbonate of *o*-hydroxybenzyl chloride. On further chlorination, the dichloro, and finally the trichloro compounds are formed.⁵³

The relative rates of chlorination of alkyl benzenes show the effect of hyperconjugation, which decreases as the number of carbon atoms in the side-chain increases. The rate of chlorination is observed to decrease with lowering of the degree of hyperconjugation. The relative rates of chlorination of benzene and some alkylated benzenes in 90% acetic acid are as follows: benzene 29, toluene 100, ethylbenzene 84, isopropylbenzene 57, *tert*-butylbenzene 32.

An exceptional behavior is shown by isopropylbenzene, which is chlorinated in the nucleus at its boiling point, in contrast to *n*-propylbenzene, which is chlorinated in the side-chain.⁵⁴

Exhaustive chlorination of toluene under illumination in the absence of catalysts leads to the formation of octachloromethylcyclohexane, $C_6H_5Cl_6CHCl_2$.⁵⁵ Pure addition, leading to the formation of hexachloromethylcyclohexane, does not occur.

Toluene may be chlorinated by the use of sulfuryl chloride in the presence of aluminum chloride. Mono-, di-, and polychlorinated derivatives are obtained depending on the amount of sulfuryl chloride used.⁵⁶ Pentachlorotoluene may be prepared in quantitative yield by this method.

Chlorination of Naphthalene and other Polynuclear Hydrocarbons

Naphthalene reacts more readily with chlorine than benzene. Initial products of the reaction in the cold are addition compounds, naphthalene dichloride, $C_{10}H_8Cl_2$, and naphthalene tetrachloride, $C_{10}H_8Cl_4$. These compounds lose hydrogen chloride on heating and form substitution products of naphthalene.⁵⁷ Dehydrochlorination may be brought about more effectively by heating these addition compounds with alcoholic caustic. Naphthalene dichloride gives α -chloronaphthalene almost exclusively when dehydrochlorinated, while naphthalene tetrachloride yields 1,3-, 1,4-, and 2,3-dichloronaphthalenes. On further chlorination of the resulting halogen substitution products, addition compounds are again formed, which may be similarly dehydrogenated to substitution products. Mono-, di-, and tetrachloronaphthalenes have been prepared in this manner.⁵⁸ It is understandable that on chlorination under conditions that are not rigidly controlled, a mixture of products of varying nature, including addition and substitution products, will result.

Hydrogen atoms in naphthalene may be replaced with chlorine by carrying out the reaction between the halogen and the hydrocarbon in the presence of chlorine carriers, such as antimony chloride.⁵⁹ The first stage of the chlorination involves the formation of the α -compound with only minute amounts of the β -isomer. On further halogenation, the chlorine again enters the remaining α -position. Exhaustive chlorination finally results in the formation of perchloronaphthalene, $C_{10}Cl_8$. Hexachlorobenzene, hexachloroethane, and carbon tetrachloride are formed when the octachloro compound is further chlorinated.

α -Chloronaphthalene may be obtained also by the action of phosphorus pentachloride on naphthalene-1-sulfonic acid, as well as through the reaction of the same reagent with α -nitronaphthalene,⁶⁰ and with β -naphthol. The compound may be prepared also from α -naphthylamine by diazotization and replacement of the diazo group with chlorine. β -Chloronaphthalene may similarly be obtained from β -naphthylamine through diazotization and replacement of the diazo group, and by the action of phosphorus pentachloride on naphthalene- β -sulfonic chloride⁶¹ or on β -naphthol.

Dichloronaphthoquinone, treated with phosphorus pentachloride, gives 1,2,3,4,5-pentachloronaphthalene; treatment of the latter with nitric acid results in the formation of tetrachlorophthalic acid.

Naphthalene has been chlorinated by use of sodium chlorate as follows: The compound was mixed by grinding with the calculated quantity of the chlorate, the mixture was dampened with a little water to a thick paste and broken into small lumps which were dropped one by one into concentrated hydrochloric acid. By using a 50% excess of the chlorate over the amount theoretically required for the formation of the tetrachloro compound, the latter was obtained as the principal product.⁶²

Chlorine, reacting with *anthracene*, first forms a loose addition compound, a 9,10-dichloride, which is converted to a mono substitution product when it is heated or treated with alkalis. On further chlorination, the dichloride is converted to 9,10-dichloroanthracene,⁶³ and finally to 9,10-dichloroanthracene tetrachloride, a compound which is readily reduced to 9,10-dichloroanthracene. Octachloroanthracenes are formed when dichloroanthracene tetrachloride is vigorously chlorinated, continued halogenation finally resulting in the formation of perchlorobenzene and carbon tetrachloride.⁶⁴

The dichloro addition compound of anthracene is obtained readily by passing gaseous chlorine through a solution of anthracene in carbon disulfide cooled to 0° . The compound decomposes at room temperature to 9-chloroanthracene and hydrogen chloride. 9,10-Dichloroanthracene is formed on chlorinating anthracene at 100° .

1,2-Dichloroanthracene is formed when 1,2,3,4-tetrachloroanthracene is heated with zinc dust and ammonia.

Oxidation of halo anthracenes causes the replacement of the meso halogen atoms with oxygen, while the chlorine atoms attached to the benzenoid nuclei remain intact.

Phenanthrene gives 9,10-dichloro- and 2,9,10-trichlorophenanthrene when treated with chlorine;⁶⁵ a dichlorophenanthrene tetrachloride is also formed simultaneously. Continued chlorination causes breakdown of the phenanthrene skeleton with the formation of perchlorobenzene.

9-Chlorophenanthrene is formed by removing the elements of hydrogen chloride from 9,10-phenanthrene dichloride.⁶⁶

2,9,10-Trichlorophenanthrene results when 9,10-phenanthraquinone is treated with phosphorus pentachloride.⁶⁷

When phenanthrene is treated with antimony pentachloride, a vigorous reaction ensues and tetrachlorophenanthrene is formed.⁶⁸

Octachloroanthracene gives hexachlorobenzene and carbon tetrachloride when further chlorinated.

Fluorene, on chlorination, gives 2-chlorofluorene and 2,7-dichlorofluorene.⁶⁹

2-Chlorofluorene is obtained from the 2-amino compound via the diazonium derivative.⁷⁰ 9-Chlorofluorene results when fluorene alcohol is treated with phosphorus pentachloride.⁷¹ 2,7,9,9-Tetrachlorofluorene results when fluorene-2,7-disulfonic acid is treated with phosphorus pentachloride.⁷²

Acenaphthene gives 5-chloroacenaphthene when subjected to the action of chlorine.⁷³ 3-Chloronaphthalene is obtained from 3-aminoacenaphthene by the diazotization route.

Chlorination of Phenols

Mono-, di-, and trichlorophenols may be obtained by the direct chlorination of phenols under controlled conditions in an anhydrous solvent, such as glacial acetic acid, carbon tetrachloride, etc. Chlorination may be effected also in the absence of a solvent. The halogen enters the *ortho* or *para* position with respect to the hydroxyl group. This holds true also for the homologs of phenol, because the hydroxyl group exerts a greater directive effect than alkyl groups. At low temperatures *para* chlorophenols are obtained almost exclusively, but at 150 to 180° only *ortho* halophenols are formed.

Polyhalogenation takes place if the chlorination is prolonged. The formation of polychloro compounds is favored by the presence of catalysts. Thus, phenol, subjected to the action of chlorine at 70–75° in the presence of ferric chloride or iodine, is converted to 2,3,4,6-tetrachlorophenol. Pentachloroanisole is obtained from anisole by chlorination at 60° in the presence of iodine.⁷⁵

o-Chlorophenol may be prepared by conducting gaseous chlorine over phenol heated at 150–180°.

Trichlorocresol gives 1-methylpentachloro-3,4-diketotetrahydrobenzene,



when it is further chlorinated at an elevated temperature.⁷⁶

Hydroquinone is converted to 2,3-dichlorohydroquinone when it is treated with the calculated quantity of chlorine in acetic acid solution at 70°. A little of the 2,5-dichloroisomer also forms simultaneously.⁷⁷

Orthochlorophenol may be obtained in the pure form by replacing one sulfonic group in benzene-2,4-disulfonic acid with chlorine, then removing the remaining sulfonic group.⁷⁸

Phenols may be readily chlorinated by the action of the calculated quantity of potassium permanganate on phenol in solution in an excess of dilute hydrochloric acid.⁷⁹

Sulfuryl chloride, SO_2Cl_2 , is useful as a mild chlorinating agent for phenols.⁸⁰ Monochloro derivatives are obtained when the free phenols or their alkali metal

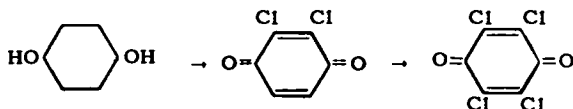
salts in solution are treated with sulfuryl chloride. Chlorination proceeds the more readily the greater the number of hydroxyl groups attached to the nucleus. Polychlorinated compounds are obtained when solid anhydrous alkali phenolates are treated with this reagent; sodium phenolate, for example, gives 2,3,4,6-tetrachlorophenol.

m-Cresol is chlorinated more readily than *p*-cresol, and by making use of just a sufficient amount of sulfuryl chloride, it is possible to chlorinate the *meta* isomer preferentially.⁸¹

Pyrocatechol, reacting with one molecular equivalent of sulfuryl chloride, gives the *para* mono chloro derivative, together with a little of the *ortho* compound. Reaction with two molecular equivalents results in the formation of the 4,5-dichloro product.⁸²

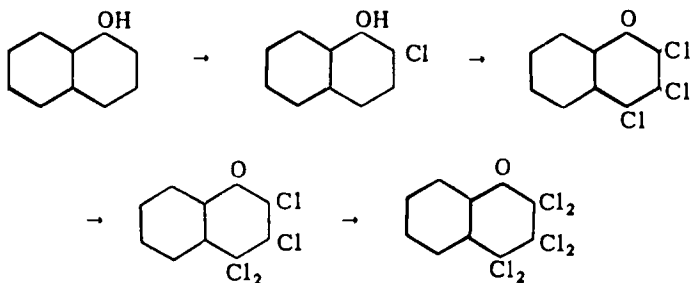
2,4-Dichlorohydroquinone has been obtained from hydroquinone by direct chlorination in acetic acid at ordinary temperature.⁷⁷ On chlorinating hydroquinone at 70° with two equivalents of chlorine, tetrachlorohydroquinone is formed, together with small amounts of 2,3- and 2,5-dichloroquinone.

When sulfuryl chloride is added to an ethereal solution of hydroquinone cooled to 0°, *γ*- or *o*-dichloroquinone, and finally tetrachloroquinone is formed.⁸³

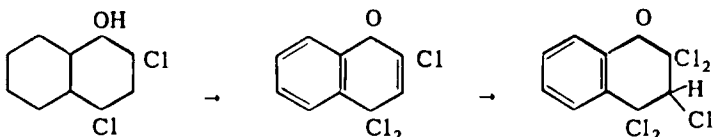


p-Aminophenol, heated with sulfuryl chloride under reflux at 40-45° for four days, gives 1-hydroxy-2,3,5,6-tetrachloro(4-dichloroamino)benzene.⁸⁴

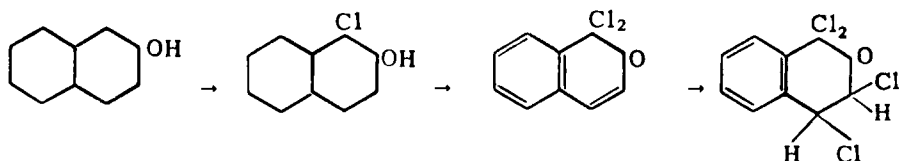
Direct chlorination of *α*-naphthol in glacial acetic acid gives first a 2,4-dichloro substitution product, then a 2,3,4-trichloro derivative. On further chlorination, tetrachloro-*α*-ketodihydronaphthalene and finally hexachloro-*α*-ketotetrahydronaphthalene are formed:⁸⁵



Tetrachloroketodihydronaphthalene, treated with dilute alcoholic sodium hydroxide, gives 2,3-dichloro-*α*-naphthoquinone. Halogenation may also proceed in another direction, leading to the formation of trichloro-*α*-ketodihydronaphthalene and pentachloro-*α*-ketotetrahydronaphthalene:



Halogenation of β -naphthol in the same manner results in the formation of 1-chloro- β -naphthol, then successively dichloro- β -ketodihydronaphthalene and tetrachloroketotetrahydronaphthalene:



Substitution of halogens for hydrogen in β -naphthol takes place successively in 1, 3, 6, and 4 positions.

2-Chloro-1-naphthol is obtained by the action of alkaline hypochlorite on α -naphthol.⁸⁶ 4-Chloro-1-naphthol is obtained with sulfuryl chloride,⁸⁷ and dichloronaphthoquinone with potassium chlorate.⁸⁸

Dichloronaphthalenes may be prepared from naphtholsulfonic acids.⁸⁹ Chloronaphthalenes are intermediate products in this reaction.

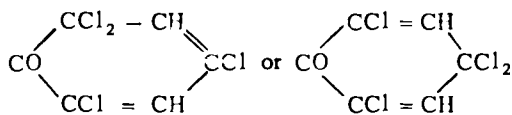
On boiling 2,3,4-trichloronaphthol with an acetic acid solution of hydrogen iodide, 3-chloronaphthol is obtained.

Halogen atoms at positions 2 and 4 in α -naphthol are activated by the hydroxyl group, and may be readily replaced with hydrogen by heating with hydriodic acid. The hydroxyl group in β -naphthol exerts an activating influence on halogens at positions 1, 6, and 3 with maximum effect at position 1 and least at position 3.

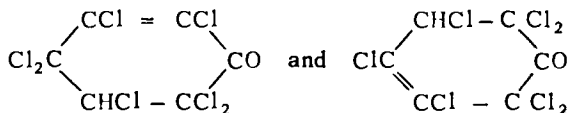
Chlorination of *phenol ethers* takes place quite readily. Alkyl groups joined to the oxygen cause a greater activation of the nucleus than aralkyl groups, and the greater the molecular weight of the alkyl group, the greater its activating effect. The isopropyl group causes a particularly marked activation. Other substituents present in the nucleus also exert an effect, chlorine causing a decided increase in activity, particularly if present in the ortho position.

Phenol ethers are halogenated in the nucleus by the action of phosphorus pentachloride; anisole, for example, gives *p*-chloroanisole at 30 to 70°.⁹⁰

Chlorinated phenols not capable of further substitution in the nucleus by the direct action of the halogen may react with chlorine to form addition compounds. For example, 2,4,6-trichlorophenol gives the tetrachloro compounds⁹¹



Two heptachloro derivatives of cyclohexenone

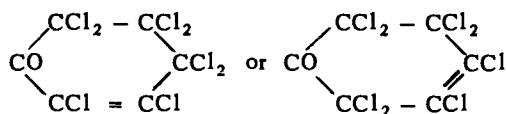


designated as α and β , are obtained from π -chloroaniline by conducting a current

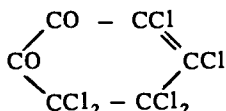
of chlorine through a solution of the compound in a mixture of acetic and hydrochloric acids. The α -compound is first to precipitate out followed by the β -compound.⁹²

Only the positions 2, 4, and 6 in resorcinol may be chlorinated by substitution. The fully substituted compound, the trichloride, is capable of adding two or four atoms of chlorine to form a pentachloro and heptachloro derivative. These are readily reconverted to trichlororesorcinol by treatment with stannous chloride.⁹³ A hexachloro derivative is obtained on chlorinating 3,5-dihydroxybenzoic acid.⁹⁴

Fully chlorinated phenols also show this property. Pentachlorophenol, for example, is capable of adding three atoms of chlorine to form an octachloro-cyclohexanone,



Tetrachloropyrocatechol gives hexachlorocyclohexadiene,



This compound is converted to hexachlorobenzene when it is heated with phosphorus pentachloride.⁹⁵

Aromatic thiophenols are first converted to disulfides when subjected to the action of chlorine in acetic acid solution, and they are finally converted to sulfochlorides:⁹⁶



Chlorination of Quinones

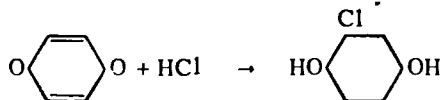
The method of direct halogenation with chlorine is employed to a limited extent in the preparation of chloroquinones. Certain anthraquinone derivatives may be readily obtained by this method.⁹⁷ Halogenation of anthraquinone itself proceeds with difficulty, but hydroxy and amino derivatives of anthraquinone are readily chlorinated.

p-Dichloroanthrarufin is obtained by conducting a current of chlorine through a boiling acetic acid solution of anthrarufin, or through an aqueous sulfuric acid solution of the compound heated at 140°. ⁹⁸ Chlororufigallic acid is obtained similarly from rufigallic acid.⁹⁹ Alizarin may be converted to 3-chloroalizarin by direct chlorination in slightly acid aqueous suspension.¹⁰⁰ Anthraflavic acid may be converted to dichloroflavic acid by chlorination at 120° in strong sulfuric acid;¹⁰¹ and chrysazin is converted similarly to *p*-dichlorochrysazin.¹⁰²

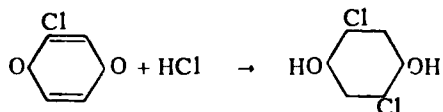
When anthraflavic acid is chlorinated at 110° in suspension in a solution of calcium or magnesium chloride, a hexachloro addition product results.¹⁰³ On heating this compound with phenol or cresol, it is converted to a trichloro substitution product; heating with aniline results in the formation of a dichloro derivative.¹⁰⁴

Alkaline hypochlorites cause the destruction of many hydroxyanthraquinones, such as alizarin, anthrapurpurin, flavopurpurin, purpurin, etc. Non-dyeing α -hydroxyanthraquinones, such as erythrohydroxyanthraquinone, anthrarufin, and chrysazin, are also decomposed by hypochlorites. β -Hydroxyanthraquinones, on the other hand, give chlorinated products when treated with alkaline hypochlorites.¹⁰⁵ The reaction proceeds at ordinary temperature.

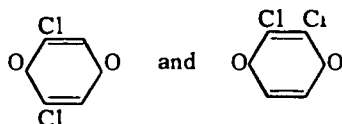
Quinone reacts with hydrochloric acid to form chlorohydroquinone:



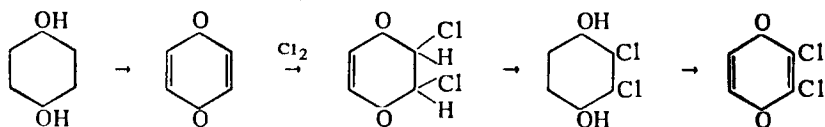
Oxidation of chlorohydroquinone with potassium dichromate and dilute sulfuric acid results in the formation of monochloroquinone. Chloroquinone also reacts with hydrochloric acid forming dichlorohydroquinone:



This can again be converted to the corresponding dichloroquinone, which in turn reacts with hydrogen chloride to form trichlorohydroquinone. The cycle of operations may be repeated to obtain in turn trichloroquinone, tetrachlorohydroquinone, and finally tetrachloroquinone.¹⁰⁶ This method thus makes it possible to prepare all the chloroquinones except β - and γ -dichloroquinones.



The former is obtained in almost theoretical yield through the oxidation of 2,4,6-trichlorophenol with nitrous acid,¹⁰⁷ or with chromic acid and glacial acetic acid at room temperature.¹⁰⁸ γ -Dichloroquinone, also termed σ -dichloroquinone, results through the reaction of hydroquinone in ethereal solution with sulfuryl chloride at 0°. ¹⁰⁹ Hydroquinone is first oxidized by the reagent to quinone, which is then dichlorinated; the dichloro compound undergoes rearrangement to dichlorohydroquinone, and this is finally oxidized to γ -dichloroquinone:

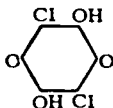


Tetrachloroquinone or *chloranil* may be prepared best in the laboratory by chlorinating hydroquinone with a mixture of potassium chlorate and hydrochloric acid. The crude product thus prepared contains some trichloroquinone, but this can be converted to tetrachloroquinone by heating with hydrogen chloride and oxidizing the resulting tetrachlorohydroquinone with potassium dichromate.¹¹⁰

The compound may be prepared also by the action of aqua regia on *p*-phenylenediamine or hydroquinone;¹¹¹ also through the action of this reagent on phenol, chlorinated phenols, salicylic acid, and sulfanilic acid.¹¹² Chranil has been prepared also from nitraniline by first converting this to dichloronitraniline, reducing the latter to dichlorophenylenediamine, and finally subjecting this to the action of potassium chlorate and hydrochloric acid.¹¹³

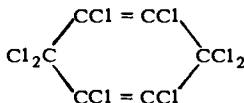
Monochloroquinone is formed on boiling 4-chloro-1,2-dinitrobenzene with sodium hydroxide solution.¹¹⁴

p-Dichloro-*p*-hydroxyquinone,

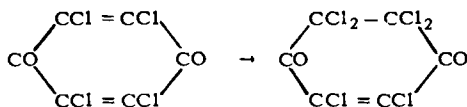


results on treating tri- and tetrachloroquinone with caustic solution and precipitating the free hydroxy compound with hydrochloric acid.¹¹⁵ Trichlorohydroxyquinone has been prepared from chloranil by treatment with alkali.¹¹⁶ Two isomeric dimethoxy- and diethoxydichloroquinones result when chloranil is treated with potassium methoxide or ethoxide.¹¹⁷

Chloranil is converted to hexachlorobenzene when strongly heated with phosphorus pentachloride, or to hexachlorobenzene dichloride,



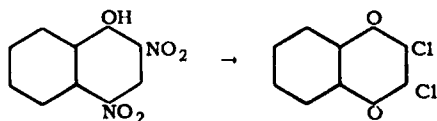
by carrying out the reaction slowly at 135–140°. Chloranil, heated with manganese dioxide and hydrochloric acid, takes up two atoms of chlorine to form hexachlorocyclohexenedione, and this, on treatment with alkalis breaks down to the alkali metal salt of dichloromaleic acid and trichloroethylene:



Hexachlorocyclohexenedione has also been obtained through the chlorination of *p*-aminophenol.¹¹⁸

Some chlorinated quinones have been prepared by the oxidation of chlorinated aromatic compounds. *o*-Chloro-*p*-aminophenol is converted to monochloroquinone by oxidizing its sulfate in slightly acid medium with potassium dichromate.¹¹⁹ Halotoluquinones, haloxyloquinones, and halothymoquinones have been prepared through the oxidation of the corresponding halophenols.¹²⁰ Dichloro- α -naphthoquinone has been obtained from chloronaphthalene tetrachloride by oxidation with nitric acid.¹²¹

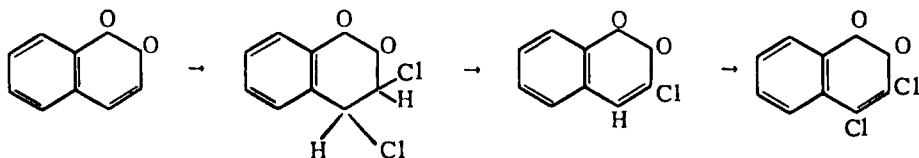
Dichloro- α -naphthoquinone is obtained more conveniently by treating Martius Yellow with a mixture of potassium chlorate and hydrochloric acid.¹²²



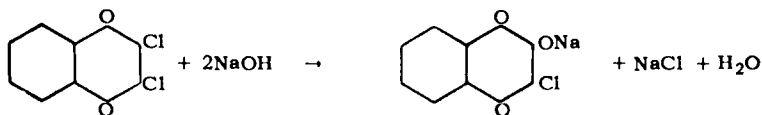
The compound is also formed through the oxidation of other chlorinated naphthalenes by the action of chromic acid;¹²³ by treating α -naphthol with a mixture of potassium chlorate and hydrochloric acid;¹²⁴ through the chlorination of 1,4-diaminonaphthol, or naphthoquinone.¹²⁵ Cold dilute sodium hydroxide solution converts dichloro- α -naphthoquinone to 2-hydroxy-3-chloro- α -naphthoquinone.¹²⁶

Several other chlorinated derivatives of α -naphthoquinone have been prepared.¹²⁷

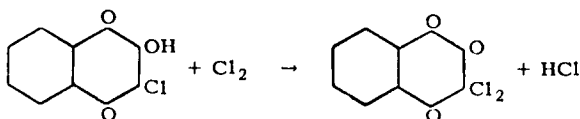
The reaction of α -naphthoquinone with chlorine proceeds in steps resembling those observed in the chlorination of naphthalene. In glacial acetic acid solution, an addition product, α -naphthoquinone dichloride, is first formed; this loses a molecule of hydrogen chloride and is thus transformed into a monochloro substitution product. Continued chlorination of the monochloro compound results in the formation of dichloronaphthoquinone.¹²⁸ The reaction of β -naphthoquinone with the halogen also proceeds in a similar manner, resulting first in the formation of an addition compound followed by dehydrohalogenation to a monochloro compound, and finally of dichloro- α -naphthoquinone by a process of substitution.¹²⁹



Sodium hydroxide reacts with α -dichloronaphthoquinone slowly in the cold to form the sodium salt of chlorohydroxynaphthoquinone:¹³⁰



Chlorine converts the free hydroxy compound to 1,2,4-triketo-3,3-dichlorotetrahydronaphthalene:¹³¹



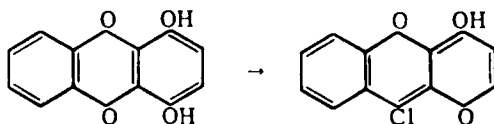
Dichloro- β -naphthoquinone is converted by cold dilute sodium hydroxide solution to an acid of the indene series.

Many *halo anthraquinones* have been obtained from halo anthracenes by oxidation. Halogen atoms attached to the meso carbon atoms are removed in the

process, others remaining unaffected. Thus 1,2-dichloroanthracene gives 1,2-dichloroanthraquinone, 2,9,10-trichloroanthracene gives 2-chloroanthraquinone, and 1,3,9,10-anthracene gives 1,3-dichloroanthraquinone.¹³²

Chlorinating agents have been used in the preparation of certain haloquinones. An example of the use of sulfuryl chloride in the preparation of γ -dichloroquinone has been cited. 4-Chloro-1-hydroxyanthraquinone and its derivatives have been obtained by heating 1-hydroxyanthraquinone or its derivatives with sulfuryl chloride in the presence of a catalyst such as iodine.¹³³ Aminoanthraquinone and aminoanthraquinonecarboxylic acids are chlorinated by heating with sulfuryl chloride.¹³⁴ Monochloro- β -aminoanthraquinone has been obtained by this method from β -aminoanthraquinone, and tetrachloro-1,5-diaminoanthraquinone from 1,5-diaminoanthraquinone. Octachloroanthraquinone is formed on heating anthraquinone with *antimony pentachloride* and a little iodine.¹³⁵ This reagent converts 1,4,5,8-tetrachloroanthraquinone largely into 1,2,3,5,6,7,8-heptachloroanthraquinone.¹³⁶ Dichloroanthraquinone heated with six times its weight of the reagent is converted to tetrachloroanthraquinone.¹³⁷ 1-Chloro-5-nitroanthraquinone results when a solution of sodium chlorate is added to a boiling solution of 5-nitroanthraquinone in dilute hydrochloric acid. 1-Chloro-8-nitrohydroquinone may be prepared similarly from the 8-nitro derivative.³²⁸

Hydroxyl groups in certain quinones, viz., hydroxyanthraquinones, are replaceable with chlorine atoms by treatment with phosphorus pentachloride or trichloride.¹³⁸ On treating quinazarin with thionyl chloride, 10-chloro-1-hydroxy-4,9-anthraquinone is obtained:¹³⁹



Sulfo groups in sulfonic acids of the anthraquinone series, including halo- and nitroanthraquinonesulfonic acids, are characterized by a great mobility, and are readily replaced with chlorine under the action of nascent halogen. α -Chloroanthraquinone may be obtained in this manner in excellent yield from anthraquinone- α -sulfonic acid. The sulfonic group in β -sulfonic acids is replaced with greater difficulty, and the expected chloro compounds are obtained in unsatisfactory yield from these, because some substitution of hydrogen atoms attached to the anthraquinone nucleus takes place in the course of the reaction.

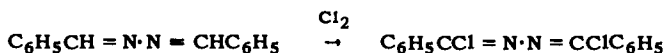
Chlorinated Aldehydes and Ketones

Chloro-substituted benzaldehydes are prepared from chlorobenzylidene chlorides by hydrolysis with aqueous oxalic or sulfuric acid.¹⁴⁰ They are prepared also by the oxidation of chlorinated cinnamic acids. The reaction of chlorine with benzaldehyde results in the replacement of the hydrogen of the aldehyde group with the formation of benzyl chloride. *p*-Hydroxybenzaldehyde, on the other hand, has been converted to *m*-chloro- and *m,m*-dichloro-*p*-hydroxybenzaldehyde by the action of chlorine in chloroform or acetic acid solution.¹⁴¹

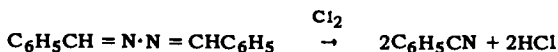
Benzaldehyde has been converted to 2,5-dichlorobenzaldehyde by treatment below 60° with antimony pentachloride in the presence of iodine.¹⁴² This method has been employed for the preparation of pentachlorobenzal chloride.¹⁴³

Piperonal has been chlorinated successfully by treatment with sulfuryl chloride in the cold.¹⁴⁴

Benzalazine, chlorinated in the cold in carbon tetrachloride solution, is converted almost quantitatively to dibenzhydrazide chloride;³²⁹

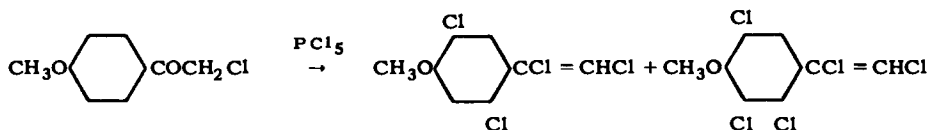


Benzonitrile is formed almost exclusively if the reaction is carried out in warm benzonitrile:



p-Chlorinated aromatic *ketones* are obtained through the reaction of acyl chlorides with chlorinated aromatic bodies in the presence of aluminum chloride.¹⁴⁵

Phosphorus pentachloride has been employed for the replacement of the carbonyl oxygen atom in aromatic ketones with chlorine. Ring chlorination may take place by the action of this reagent with ketones. Nuclear substitution has been observed, for example, when *p*-methoxyphenacyl chloride was heated with phosphorus pentachloride over a free flame;¹⁴⁶



Chlorinated Aromatic Acids

Chlorinated aromatic acids may be prepared by the action of chlorine on the acids. Halogenation does not take place readily, however, and benzoic acid, for example, is attacked by chlorine only at 150°.¹⁴⁷ The first halogen atom enters the *meta* position with respect to the carboxyl group. Chlorobenzoic acid and its derivatives are obtained from anthranilic acid and its derivatives via the diazotization route. *p*-Chlorobenzoic acids are readily obtained through the oxidation of *p*-chlorotoluene and its derivatives.

3,5-Dichloro-2-aminobenzoic acid is obtained in 75% yield on treating *anthranilic acid* in glacial acetic acid solution with chlorine. Similar treatment of *p*-aminobenzoic acid results in the formation of 3,5-dichloro-4-aminobenzoic acid in 35% yield, together with considerable amounts of 2,4,6-trichloroaniline.¹⁴⁸

Phthalic anhydride has been chlorinated by the direct action of the halogen on the anhydride in solution in fuming sulfuric acid in the presence of iodine.¹⁴⁹ The degree of chlorination achieved depends on the SO₃ content of the acid, the reaction temperature, and the amount of chlorine used. Tetrachlorophthalic anhydride is formed on chlorinating a solution of 10 kg of phthalic anhydride in 30 kg of acid of 50–60% SO₃ content in the presence of 0.5 kg iodine at a temperature gradually increasing from 50 to 200°.

The action of chloride of lime on *salicylic acid* usually results in the formation of chlorinated phenols. Chlorinated salicylic acids have been obtained, however, by treating a well-cooled solution of dipotassium salicylate with a molecular equivalent of potassium hypochlorite, and pouring the liquid into a mixture of ice and dilute sulfuric

acid.¹⁵⁰ Dichlorosalicylic acid may be obtained as the principal product of the reaction by using three molecular proportions of potassium hypochlorite.

Many halogenated acids have been prepared by indirect methods, such as oxidation of halogenated toluenes; replacement of amino groups with hydrogen by the diazotization route; substitution of the amino groups in halogenated amines with the cyano group, also via the diazo compound, and subsequent hydrolysis of the nitrile formed. Some halogenated acids have been made through the replacement of the nitro group in chloronitro compounds with a carboxyl group by reaction with alcoholic potassium cyanate at 200–230°.¹⁵¹

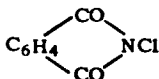
N-Chloro Amides

A hydrogen atom in the amido group in acid amides may be replaced by treatment with chlorine or with certain chlorinating agents.

Benzamide, suspended in water and treated with chlorine, is converted to benzoyl chloramide, $C_6H_5CONHCl$.¹⁵² Phenylureas treated similarly give nuclearily chlorinated derivatives.¹⁵³

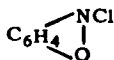
N-Chloroacetanilide precipitates out on adding a concentrated aqueous solution of chloride of lime to one of acetanilide containing acetic acid in excess. The compound rapidly undergoes rearrangement to p-chloroacetanilide on treating with hydrochloric acid.¹⁵⁴

N-Chlorophthalimide,



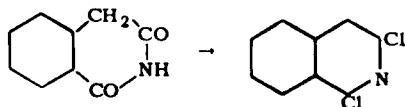
may be obtained by treating an aqueous suspension of the amide with chlorine.¹⁵⁵ The procedure is to suspend 50 parts of finely powdered phthalimide in 500 parts of water and to treat the suspension with chlorine. The best method of preparation consists, however, in treating the imide in aqueous suspension with the required quantity of freshly made hypochlorous acid at room temperature, whereupon, phthalimide chloride separates out in flocks.

In the preparation of quinone chloroimide,



from p-aminophenol by treatment with chloride of lime, it is necessary to eliminate the chloroimide from the sphere of action of calcium hypochlorite by use of a suitable solvent, such as ether.¹⁵⁶

Treatment of homo-o-phthalimide with phosphorus oxychloride at 150–170° results in the formation of dichloroisoquinoline:¹⁵⁷



Derivatives of homo-o-phthalimide behave similarly.

Benzoquinone chloroimides,¹⁵⁸ typified by $O = C_6H_4 = NCl$, are formed through the action of chloride of lime solution on a p-phenylenediamine hydrochloride. Benzoquinone-dichloroimides are little investigated. Benzoquinonedichloroimide, $ClN = C_6H_4 = NCl$, is

formed by the action of chloride of lime solution on *p*-phenylenediamine hydrochloride. The compound decomposes at 124°.

Chlorination of Aromatic Amines

Chlorine reacts readily with aromatic amines or their salts, giving nuclearly chlorinated amines. When chlorine water is allowed to react with aniline salts, the halogen enters at 2, 4, and 6 positions.¹⁵⁹ Primary amines are halogenated with great ease and the isolation of mono-substitution products is often impossible.

Direct chlorination of *p*-nitraniline with gaseous chlorine at room temperature results in the formation of resinous products. *o*-Chloro-*p*-nitraniline has been prepared, however, by dissolving 34.5 kg of *p*-nitraniline in 200 kg of concentrated hydrochloric acid, or the same amount of 60% sulfuric acid, adding 400 kg of ice, cooling the mixture to -10°, and passing chlorine through the liquid, without allowing the temperature to rise above 0°. The reaction is complete when a weight increase of 18 kg is attained. The chloro compound is precipitated quantitatively on diluting the reaction mixture with water.

Dichloroaniline has been obtained by dissolving nitraniline in a large excess of hydrochloric acid, cooling the solution strongly, and passing chlorine until the odor of the halogen is perceptible and no further yellow precipitate is thrown out of the solution.¹⁶⁰

Dichloro- β -naphthylamine has been prepared by suspending β -naphthylamine in 50 times its weight of sulfuric acid, cooling the mixture with ice, and passing two molecular proportions of chlorine through the liquid. The dichloro compound is precipitated out by pouring the solution in ice water; it is washed with ammonia, and purified by crystallization from alcohol, or by steam distillation.¹⁶¹

Halogenation of primary and secondary amines is best effected in acetic acid solution. Halogenation also proceeds satisfactorily in aqueous hydrochloric acid. Halogenation of such amines may be carried out in solution in alcohol, ether, chloroform, and carbon disulfide.

It is often necessary to protect the amino group in aromatic amines by *acylation*, and to carry out the chlorination at a low temperature in order to avoid side reactions. *Ortho* and *para* chloro derivatives are the first products of chlorination, and these may be converted to *o,p*-dichloro compounds.

The reaction may be carried out by passing the required amount of chlorine through a solution or suspension of the acylated amine in glacial acetic acid containing an equimolecular amount of anhydrous sodium acetate. The reaction proceeds smoothly at ordinary temperature. The chlorinated compound may be precipitated by diluting the solution with water.¹⁶²

2-Acetamino-1,4-xylene, treated with chlorine in the cold, gives the 5-chloro derivative.¹⁶³

Acetyl derivatives of primary aromatic amines may be chlorinated by use of the required quantity of hypochlorous acid. The reaction is carried out by adding hypochlorite to the solution of the compound in acetic acid.

As an example of the procedure, 5 parts of acetanilide are dissolved in a mixture of 10 parts of acetic acid and 10 of alcohol by warming. The mixture is diluted with 100 parts of water, heated to 50°, and 100 parts of a cold 10% solution of calcium hypochlorite solution are added slowly with good agitation. The monochloroacetanilide formed precipitates out as a white crystalline solid, and may be purified by crystallization from acetic acid or alcohol.

By carrying out the reaction first at 90°, then at about 60-70° in dilute acetic acid solution, and using four times as much hypochlorite solution, dichloroacetanilide is obtained in the form of the complex compound with hypochlorous acid. This complex may be decomposed by dissolving it in ether, drying the solution with calcium chloride, and allowing it to evaporate to dryness.

Nascent chlorine, generated by the interaction of potassium chlorate and hydrochloric acid, has also been used for the chlorination of aromatic amines and acylated amines.¹⁶⁴ *m*-Acetotoluide has been converted by this method to monochloro-*m*-acetotoluide.

Substituents in the nucleus are occasionally replaced during halogenation. For example, chlorination of *p*-bromoaniline gives a mixture of dichlorobromoaniline and trichloroaniline, and chlorination of 2,4-dibromoaniline results in the formation of tribromoaniline and dichlorobromoaniline.¹⁶⁵

Aniline and other aromatic amines, chlorinated in concentrated sulfuric acid, are converted to *meta* chlorinated derivatives. This is in contrast to the results of chlorination of acylated amines in acetic acid solution, for example, which gives *ortho* and *para* chlorinated derivatives. The explanation of this effect lies in the fact that the "ammonium" group in aniline sulfate carries a positive charge, and is therefore *meta* directing. It should be noted that chlorine and bromine are without action at room temperature on aniline in solution in 97% sulfuric acid.¹⁶⁶

It is possible to prepare *p*-chloroaniline through the reduction of nitrobenzene in strong hydrochloric acid solution. *N*-Chlorophenylamine, C_6H_5NHCl , appears to be the intermediate product, molecular rearrangement resulting in the formation of the *p*-chloro compound.¹⁶⁷

Monochloroanilines are obtained in good yield from halo nitro compounds by reduction; the latter may be prepared from nitroamino bodies via the diazo compounds.

p-Chloroanilines are obtained by heating *p*-chlorobromobenzene and its analogs with ammonia in the presence of cuprous oxide in a sealed tube at 120°.

It is usually impossible to introduce more than three halogen atoms into the nucleus of aniline and its homologs by direct halogenation. It is possible, however, to prepare more highly halogenated amines by starting with *meta* halogenated derivatives; these may be further halogenated at the 2, 4, 6, and even the 5 positions.

Amino compounds, such as aniline and anthranilic acid, have been chlorinated by use of sulfuryl chloride in benzene solution.¹⁶⁸ Yields are considerably improved by treating the hydrochlorides of the bases rather than the free amine.

Chlorination of Nitro Compounds

Nitrated compounds are, in general, chlorinated with difficulty. The chlorination of nitrobenzene requires careful operation, and can be successfully carried out only in the complete absence of moisture; even small traces of moisture prevent chlorination or greatly retard it. Nitrobenzene may be fully dehydrated by heating at 80-100° for several hours while a stream of dry air is passed through it. Chlorination is best effected in the presence of a carrier such as iron or aluminum chloride.

o-Nitrotoluene may be converted by direct chlorination to *o*-chloro-*o*-nitrotoluene. Further chlorination does not result in the formation of *o*-chloro-*o*-nitrobenzyl chloride. This is in contrast to the behavior of the chloronitro compound toward bromine with which it reacts to form *o*-chloro-*o*-nitrobenzyl bromide.¹⁶⁹

m-Nitrilaniline is readily converted to 2,4,6-trichloro-3-nitrilaniline by the action of chlorine diluted with an inert gas.¹⁷⁰ *p*-Nitrilaniline reacts smoothly with chlorine in the presence of concentrated hydrogen chloride to yield, first, 2-chloro-4-nitrilaniline, and then 2,6-dichloro-4-nitrilaniline.

Para-nitrophenol has been converted to a chloronitrophenol by means of nascent chlorine generated by the action of hydrochloric acid on potassium chlorate.¹⁷¹

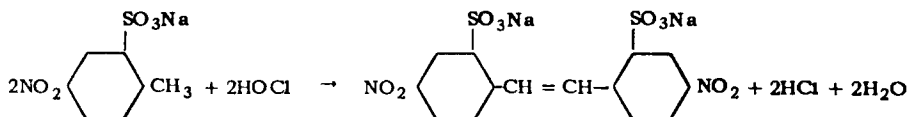
One or both nitro groups in *m*-dinitrobenzene may be replaced with chlorine under the action of this element.

Chlorination of nitrobenzene may be effected by use of antimony trichloride.¹⁷²

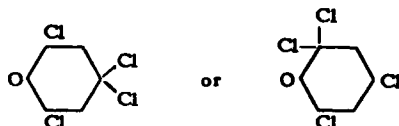
Chlorination of Sulfonic Acids

The sulfonic group in *phenolsulfonic acids* is almost invariably replaced with a chlorine atom on chlorination; in many instances one or more additional chlorine atoms enter the nucleus simultaneously. The procedure is to pass chlorine into the phenolsulfonic acid solution, whereupon the chlorinated product generally precipitates out. The behavior of aminosulfonic acids is similar to that of phenolsulfonic acids. The yield of the halogenated compound is often quantitative with monosulfonic acids, moderately good with disulfonic acids, and poor with trisulfonic acids. 5-Chloro-*o*-cresol is obtained from *m*-cresol-5-sulfonic acid, 2,4,6-trichlorophenol from phenol-*p*-sulfonic acid, 2,6-dichloro-*m*-cresol from *m*-cresol-6-sulfonic acid, 3,5-dichloro-*p*-cresol from *p*-cresol-3,5-disulfonic acid, 2,6-dichloro-*p*-nitrophenol from *p*-nitrophenol-*o*-sulfonic acid, and 2,5-dichlorosalicylic acid from salicylic-5-sulfonic acid. It would appear that methyl groups or halogen atoms present in the sulfonic acid hinder the replacement of the sulfonic group with chlorine.¹⁷³ Sulfonic acids derived from *ortho*-, *meta*- and *para*-hydroxybenzoic acids lose the sulfo group on chlorination. 2-Nitrophenol-4-sulfonic acid in alcoholic solution gives 4,6-dichloro-2-nitrophenol with an excess of chlorine, although a 6-chloro derivative of the sulfonic acid has been obtained by carrying out the halogenation with a limited amount of chlorine.³³⁰

Phenol-*p*-sulfonic acid may be chlorinated without loss of the sulfo group by carrying out the halogenation in nitrobenzene solution.³³¹ The 2,6-dichloro compound is the main product of the reaction. The 2,3-dichloro compound has been prepared similarly from 4,6-disulfonic acid.³³² If a methyl group is present in a nitrated aromatic sulfonic acid in the *para* position to the nitro group, reaction with hypochlorous acid results in the formation of a dibenzyl or stilbene derivative:³³³



Exhaustive chlorination of anisole- and phenolesulfonic acids results in the formation of tetrachloroquinone and tetrachloroketodihydrobenzene,³³⁴



Catechol-4-sulfonic acid yields tetrachloro-o-quinone and orcinol disulfonic acid gives a pentachloro compound³³⁵

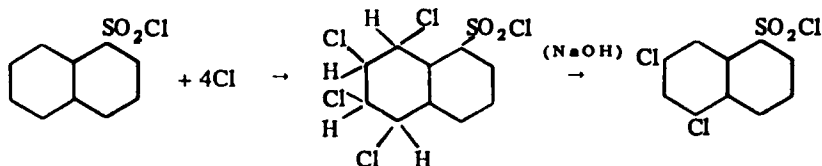
1,6-Dichloronaphthalene is the chief product from the chlorination of *naphthalene-1-sulfonic acid*, while the 2-sulfonic acid gives 50% of the 2,6-dichloro derivative. 4-Bromonaphthalene-1-sulfonic acid affords 1-chloro-4-bromonaphthalene.³³⁶

The chlorination of 1-amino-2-hydroxynaphthalene-4-sulfonic acid results in the formation of a chlorimine.³³⁷ Chloroimines are also formed without loss of the sulfo group from 1-hydroxy-2-amino-4-sulfonic acid and 1,4-diamino-6-sulfonic acid.

Nitronaphthalene- α -sulfonic acids react with chlorine or chlorinating agents to form the corresponding nitrochloronaphthalenes by replacement of the sulfonic group.³³⁸ The chlorinating agent employed most frequently is hypochlorous acid generated *in situ* by the reaction of an alkali hypochlorite with hydrochloric acid.³³⁹ 2-Acetaminonaphthalene-6-sulfonic acid is chlorinated in the 1-position without loss of the sulfonic group.³⁴⁰

The sulfonic groups in *anthraquinonedisulfonic acids* are replaceable by chlorine.³⁴¹ One or both sulfonic groups may be replaced with chlorine atoms by the proper choice of the amount of the chlorinating agent. The sulfo groups in 2-methylantraquinone-4-sulfonic acid and 2-methylantraquinone-1,4-disulfonic acid are readily replaced by chlorine when these compounds are boiled with aqueous potassium chlorate and hydrochloric acid.³⁴²

Naphthalenesulfonyl chlorides, treated with chlorine in carbon disulfide solution, are converted to addition products, the chlorine atoms all entering the unsubstituted ring.³⁴³ When the addition compounds are subjected to the action of caustic, they change to dichloronaphthalenesulfonyl chlorides or sulfonates:



1,5-Diaminoanthraquinonedisulfonic acid gives dihalo compounds with hypochlorous acid even in cold aqueous solution. The following is a satisfactory procedure: Twenty kilograms of the sodium salt of the disulfonic acid are dissolved in 1000 lit of lukewarm water and 50 kg of hydrochloric acid of 15° Bé are added. A solution of 3.2 kg of sodium hypochlorite in 20 lit of water is then added with good agitation. The reaction proceeds rapidly, the disappearance of all available chlorine from the solution indicating its completion. The chlorinated compound is precipitated by the addition of sodium chloride or sodium hydroxide.

Sulfonic acids and their salts are converted to sulfonic chlorides when treated with chlorine:



Benzene sulfinic acid does not react readily, but ortho substituted sulfinic acids react well, possibly because the *o*-sulfonic chloride is less sensitive toward water. The following presents an example of the procedure: Ten kilograms of *o*-toluenesulfinic acid are dissolved in dilute sodium hydroxide solution and chlorine is conducted through the solution as rapidly as possible, until no further precipitate is formed.

Behavior of Chlorinated Compounds

Chlorine atoms attached to an aromatic nucleus are generally unreactive and do not readily take part in exchange reactions. They may be replaced with difficulty, in general, with the cyano groups, for example, by reaction with alkali metal cyanides. This reaction proceeds, as a rule, only at elevated temperatures in the presence of metallic copper or copper salts. It is possible to replace nuclear chlorine atoms with hydrogen in the presence of catalysts. One method employed for accomplishing this result consists in shaking the chlorinated compound in the presence of hydrogen under pressure with a suspension of colloidal palladium in dilute caustic.¹⁷⁴ The presence of certain substituents in the nucleus, notably nitro groups, causes the activation of chlorine atoms. Certain nitrated chloro compounds readily exchange their halogen for various groups such as cyano, thiocyno, etc. by reaction with metallic cyanides, thiocyanates, etc.

Chlorinated aromatic compounds undergo the Wurtz-Fittig reaction rather readily. This is in contrast with the behavior of aliphatic compounds, which usually undergo this reaction with difficulty.

The chlorine in aromatic compounds in which the halogen is attached to an aliphatic side-chain is generally reactive and capable of replacement with various groups. Benzyl chloride, $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$, for example, may be readily converted to benzyl cyanide, $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$, by reaction with sodium cyanide. Substituents *X* present in the compounds $\text{XC}_6\text{H}_4\text{CH}_2\text{Cl}$ have a marked effect on the reactivity of the chlorine.¹⁷⁵ A methyl group causes an increase in the rate of hydrolysis of the chloro compound, while halogens cause a decrease. The relative rates of hydrolysis of such monosubstituted benzyl chlorides, referred to the rate of hydrolysis of benzyl chloride as one, are given in the following table:

X	Relative Rate of Hydrolysis	X	Relative Rate of Hydrolysis	X	Relative Rate of Hydrolysis
<i>p</i> -CH ₃	10.6	<i>p</i> -Br	0.5	<i>m</i> -COOH	0.2
<i>o</i> -CH ₃	4.8	<i>o</i> -Br	0.3	<i>p</i> -COOH	0.16
<i>m</i> -CH ₃	1.4	<i>m</i> -Br	0.2	<i>m</i> -NO ₂	0.09
<i>p</i> -Cl	0.6	<i>p</i> -I	0.4	<i>o</i> -NO ₂	0.08
<i>o</i> -Cl	0.3	<i>o</i> -I	0.3	<i>p</i> -NO ₂	0.07
<i>m</i> -Cl	0.2	<i>m</i> -I	0.2		

It should be noted that substituents influencing the reactivity of the chlorine of

the CH_2Cl group also similarly affect the reactivity of the nuclear hydrogen which this group has replaced. A direct parallelism is observed between the ability of substituted benzyl chlorides to undergo the Friedel-Crafts reaction with benzene, and their rate of hydrolysis.¹⁷⁶ The halogen in a side-chain in an aromatic body is the more reactive the closer it is situated to the aromatic nucleus.

Chlorine atoms attached to the nucleus of phenolic compounds enhance the acidity of the latter. Pentachlorophenol is of sufficient acidity to react with sodium carbonate in the cold, although reaction proceeds slowly.¹⁷⁷ The halogen in chlorinated phenols may be replaced with the KO- group by fusion with potassium hydroxide.¹⁷⁸ Molecular rearrangements may take place, however, in the course of this reaction.

The strength of aromatic carboxylic acids is enhanced by the presence of chlorine atoms in the nucleus. A chlorine atom in the *ortho* position exerts the greatest effect, one in the *para* position the least. The dissociation constants of monochlorobenzoic acids are given below:

<i>ortho</i> chlorobenzoic acid	0.132
<i>meta</i> " "	0.0155
<i>para</i> " "	0.0093

Halobenzoic acids are readily converted to benzoic acid by reduction with sodium amalgam; some may even be reduced by heating with zinc dust and aqueous ammonia.

AROMATIC BROMINE COMPOUNDS

Methods of Bromination

The methods employed for the bromination of aromatic compounds are similar to those used for chlorination. Bromine reacts less readily than chlorine; yet in many instances the combining power of this halogen is so pronounced that when liquid bromine is added to the heated compound, little loss of the halogen, if any, is observed through the escape of unreacted bromine. The reaction is exothermic, and it is often necessary to apply external cooling to maintain the desired temperature when sufficiently large quantities of the reactants are used.¹⁷⁹ Bromination often takes place more smoothly with halogen-sensitive substances than chlorination.

Bromination in acetic acid solution is found to be a second order reaction when the concentration of bromine is very low, say 1/1000 molar or less. At a bromine concentration of about 1/50 molar the reaction changes to one of the third order, and at $M/5$ concentration it becomes one of a fourth or fifth order. This may be considered indicative of the formation of polymolecular bromine complexes.¹⁸⁰

Bromination with Elemental Bromine

Bromination reactions are often carried out with bromine dissolved in a suitable solvent. Among the solvents generally employed are water, aqueous sodium

bromide, concentrated sulfuric acid, ether, and methyl alcohol. Formic acid, glacial acetic acid, ethyl acetate, chloroform, nitrobenzene, carbon disulfide, carbon tetrabromide, and carbon tetrachloride have also been employed. The solvent influences the rate of reaction greatly. Thus, the transformation of benzaldehyde to bromobenzyl benzoate, $\text{C}_6\text{H}_5\text{COOCHBrC}_6\text{H}_5$, under the action of the halogen proceeds about a thousand times as rapidly in carbon tetrachloride solution as in chloroform or carbon disulfide.¹⁸¹

Ionizing solvents favor nuclear substitution. Acids cause an increase in the rate of bromination in proportion to their strength and concentration, although the anion also seems to have a specific effect on the velocity of halogenation.¹⁸² The use of concentrated sulfuric acid presents the advantage that it converts the hydrogen bromide formed in the reaction more or less completely to bromine through its oxidizing action. Aqueous sodium bromide possesses considerably higher solvent power for bromine, and it is possible to increase the rate of bromination in this solvent. Methyl alcohol is a more satisfactory solvent than ethyl alcohol, because it is less susceptible to attack by the halogen.¹⁸³ Methanol, if used as a solvent, should preferably be saturated with sodium bromide.¹⁸⁴ Formic acid is generally a more suitable medium for carrying out bromination reactions than glacial acetic acid.¹⁸⁵

Pyridine is employed as a solvent when brominating highly sensitive compounds.¹⁸⁶ Bromine apparently forms a loose compound with the base, $\text{C}_6\text{H}_5\text{NBr}_2$, and this compound then functions as a mild brominating agent.¹⁸⁷ This bromine-pyridine complex would appear to act as a catalyst promoting the addition of bromine to the benzene and naphthalene ring.¹⁸⁸ Monobromobenzene and α -bromonaphthalene may be prepared by brominating the hydrocarbons in the presence of a little pyridine. Quinoline and isoquinoline also form loose complexes with bromine, and may be employed for bromination reactions in the same manner as pyridine.

Bromination may often be carried out successfully by leading vapors of bromine into the substance to be brominated at room temperature. Bromination is occasionally carried out under pressure: the compound to be halogenated, together with the required amount of bromine, is placed in a sealed tube and heated at 130-150° in a bomb oven. Benzoic acid has been converted by this method to *m*-bromobenzoic acid.

In cases where bromination proceeds with difficulty, *catalysts*, or "carriers," are employed to facilitate the reaction. The catalysts generally used are aluminum bromide, aluminum chloride, iron, ferric bromide, ferric chloride, iodine, sulfur, sulfuric acid, and zinc chloride. Ferric chloride would appear to be the most satisfactory catalyst.¹⁸⁹ Catalysts are sometimes employed even when carrying out the bromination reaction under pressure. Phenyl trimethyl ammonium bromide has been converted to 3,4-dibromophenyl trimethyl ammonium bromide by heating the compound with bromine at 100-120° in a sealed tube in the presence of iron. When this reaction is carried out at 70° the 3-bromo compound is obtained.¹⁹⁰ Different compounds may sometimes be obtained, depending on the type of catalysts used. Thus, *o*-nitrotoluene gives dibromoanthranilic

acid when bromination is carried out in the presence of sulfur, and a mixture of isomeric bromonitrotoluenes with 4-bromo-2-nitrotoluenes when the reaction is carried out in the presence of iron.¹⁹¹

Excess bromine remaining in the reaction mixture after the completion of a bromination reaction may be eliminated by warming the mixture and conducting a current of steam through it. The bromine may also be removed by adding sulfurous acid or sodium sulfite, or by heating with metallic mercury.

Bromination of the Side-Chain

The side-chain in homologs of benzene may be brominated under the conditions necessary for the chlorination of the side-chain in such compounds. The reaction of bromine with toluene takes place almost instantaneously under the influence of ultraviolet radiation and results in the formation of benzyl bromide.¹⁹² Radiation near the blue end of the spectrum exerts the maximum effect.¹⁹³ Oxygen is an effective promoter of the photo-bromination of organic bodies.¹⁹⁴

o-Butyltoluene is brominated both in the side-chain and in the nucleus under the action of radiation, although *p*-bromotoluene is only brominated in the side-chain.¹⁹⁵

ω -Tetrabromo-*p*-xylene has been obtained by heating *p*-xylene with bromine first at 140°, then to 170°, and finally at 200°. ¹⁹⁶ The tetrabromide has been converted to ω -hexabromo-*p*-xylene, Br₃CC₆H₄CBBr₃, on further treatment with bromine.¹⁹⁷

Mesitylene brominated in the sunlight gives bromomesityl bromide.¹⁹⁸

Radiation inhibits bromination in some instances. This is the case, for example, with nitrocinnamic acid, which is not attacked by bromine in direct sunlight, although bromination proceeds in diffuse daylight.¹⁹⁹

Side-chain bromination may be effected also by carrying out the halogenation at a higher temperature.

The best method of preparation of *o*-xylylene bromide, BrCH₂C₆H₄CH₂Br, is to add somewhat more than three parts by weight of bromine slowly to one part of *o*-xylene heated to 125-130° under reflux, and to allow the reaction mixture to stand for 24 hours. The product may be purified by crystallization from chlorpicrin.

Tribromo-*o*-xylenol has been converted to tribromo-*p*-hydroxy-*o*-xylylene dibromide by heating the compound with bromine in a sealed tube at 130-150°. ²⁰⁰

Solvents have a definite effect on the direction of bromination of toluene.²⁰¹ The percentages of benzyl bromide obtained in various solvents are as follows: carbon disulfide, 85.2%; carbon tetrachloride, 56.6%; acetic acid, 4.0%; nitrobenzene, 2.0%.

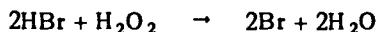
Bromination with Nascent Bromine

Bromination reactions may be carried out with nascent bromine. The reagents commonly employed for the generation of bromine are hydrogen bromide and bromic acid:



A mixture of the sodium salts of the two acids in stoichiometric proportions in aqueous solution is treated with a slight excess of sulfuric acid.²⁰² Sodium

hypobromite may also be employed as a source of nascent bromine.²⁰³ The reaction of hydrogen bromide with hydrogen peroxide is also employed for the purpose:



Monobromocodein has been obtained from codein by the action of 30% aqueous hydrogen peroxide in codein hydrobromide.²⁰⁴

The reaction of hydrobromic acid with concentrated sulfuric acid also yields nascent bromine.

Bromination with nascent bromine has been successfully carried out electrolytically. The conversion of acetone to bromoform has been effected by this method.²⁰⁵

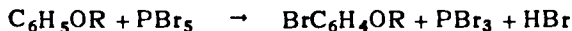
Bromination with Brominating Agents

Many bromine compounds capable of readily yielding their bromine are used as brominating agents. Substances employed for this purpose include loose combinations of tertiary bases with bromine, and of starch with this halogen, bromine monochloride, phosphorus tri- and pentabromides, sulfur monobromide, and cupric bromide.

Bromine addition compounds of various cyclic amines²⁰⁶ have been used for the preparation of a number of brominated compounds impossible to obtain by customary methods of bromination, such, for example, as monobromopyrocatechol and dibromosafrole. The pyridine addition product, $\text{C}_5\text{H}_5\text{NBr}_2$, has been utilized for the bromination of indigo.²⁰⁷ These addition products are obtained through the combination of bromine with the free bases, or through the reaction of the halogen with the salts of the bases. The loose bromine addition compound of starch has been employed for the bromination of indigo and its derivatives and analogs. The compound is prepared by grinding in a mill 50 parts by weight of starch previously dried at 100° with 18 parts by weight of bromine.

Bromine monochloride, BrCl , is a more powerful brominating agent than bromine, which in turn acts more energetically than hypobromous acid. The chloride does not act as a chlorinating agent.

Phosphorus pentabromide has been used for the bromination of phenol alkyl ethers and naphthol ether. Bromination proceeds at room temperature, well below the dissociation point of the pentabromide:



With certain phenol ethers gentle heating may be necessary.

The procedure is to add the ether in small portions to an equivalent quantity of the pentabromide in a flask protected from atmospheric moisture, shaking well after each addition; then to heat the mixture on a water bath for 10 to 15 minutes, or until the pentabromide disappears completely. The bromoether is recovered by shaking the reaction mixture with cold water and extracting the precipitated bromo compound with ether, and finally evaporating off the ether. It may be purified by distillation or crystallization. The greater portion of the phosphorus tribromide formed in the reaction may be recovered by distillation.

Phosphorus tribromide has been used in bromination reactions. The compound may be prepared by adding the required quantity of bromine slowly to a solution of phosphorus in carbon disulfide containing a little iodine.²⁰⁸ The tribromide has also been prepared in 88% yield through the action of bromine on phosphorus covered with a layer of benzene.²⁰⁹ It may be readily purified by distillation.

Sulfur monobromide, S_2Br_2 , is a useful brominating agent. Aromatic compounds subjected to the action of this reagent in the presence of nitric acid are almost invariably converted to monobromo derivatives in nearly quantitative yield. Durol gives a dibromo derivative.²¹⁰

The procedure followed in carrying out a bromination reaction with this compound is to add an excess of the reagent, slowly and with good cooling, to a mixture of the hydrocarbon with 3 parts of benzine and four of nitric acid of sp. g. 1.4. The reagent is introduced at such a rate that the addition of the total amount requires two to three hours. After completion of the reaction, the benzine layer is shaken with solid potassium hydroxide and fractionally distilled.

In the preparation of bromonaphthalene by this method, approximately 5% of nitronaphthalene is also formed; this may be eliminated by reduction to the amine with ferrous sulfate and ammonia, and extraction with an aqueous mineral acid.

Replacement of Various Groups with Bromine

Replacement reactions involving the exchange of a substituent group present in an aromatic nucleus with bromine generally proceed in a manner paralleling those involving an exchange of chlorine. When aqueous solutions or suspensions of sulfonic acids are treated with bromine, the sulfo group is, in many cases, replaced with bromine. For example, when phenolsulfonic acid is subjected to the action of bromine, 2,4,6-tribromophenol is obtained in quantitative yield.²¹¹ The sulfonic group in anthraquinone sulfonic acids is, in general, replaced quite readily with bromine; α -bromoanthraquinone may be obtained in a pure form and in high yield from anthraquinone- α -sulfonic acid by the action of bromine. The replacement of a β -sulfonic group in anthraquinones proceeds slowly and, for this reason, some substitution of nuclear hydrogens with bromine also takes place when anthraquinone β -sulfonic acids are subjected to the action of bromine. The sulfonic group in alkylated diaminoanthraquinonesulfonic acids is readily replaced with bromine. Chrisazindisulfonic acid gives with bromine tetrabromochrysazin.²¹² Both the sulfonic and carboxylic group in salicylic-5-sulfonic acid are replaceable, so that bromination of the compound results in the formation of 2,4,6-tribromophenol.

Diazo groups attached to the aromatic nucleus may be replaced with bromine atoms by Sandmeyer's method by use of cuprous bromide.²¹³ 6-Bromo-3-methoxybenzoic acid has been obtained by this method from the corresponding amino compound which was prepared by reducing 6-nitro-3-methoxybenzoic acid.

Intermolecular Transfer of Bromine

A transfer of bromine atoms from a brominated body to an aromatic body may

take place in the presence of aluminum chloride or iron chloride.²¹⁴ Such a transfer takes place, for example, from tribromophenol to benzene or toluene, resulting in the formation of monobromobenzene or monobromotoluene in good yield. Perylenes yield chlorinated derivatives under these conditions.

Bromination of Various Types of Compounds

Bromination of Aromatic Hydrocarbons

The direct bromination of *benzene* proceeds very slowly at room temperature; only half of the hydrocarbon is brominated when subjected to the action of the halogen at 30° for twenty days, and no further halogenation would appear to take place thereafter.²¹⁵ Reaction proceeds readily to completion, however, in the presence of an active catalyst or carrier.²¹⁶ Catalysts satisfactory for the chlorination of benzene are also satisfactory for the bromination of this hydrocarbon. Monobromobenzene is the principal product of the bromination of benzene in the presence of a catalyst. Toluene yields a mixture of *ortho* and *para* bromotoluenes. The reaction of bromine with boiling toluene gives first benzyl bromide, then, on further bromination, benzylidene bromide and benzotribromide.

The reaction of bromine with *naphthalene* proceeds in the same manner as that of chlorine.²¹⁷ The dibromo addition compound corresponding to the dichloro compound has never been isolated, however, and the tetrabromo compound has been obtained only by working with extreme care.²¹⁸ Under usual conditions, α -bromonaphthalene is obtained as the first product and, on continued bromination, several isomeric dibromo derivatives and higher brominated naphthalenes are obtained. Naphthalene has been converted to hexabromonaphthalene by the action of bromine in the presence of $AlCl_3$.²¹⁹

The sulfonic bromide group in naphthalene derivatives containing this residue is readily replaced with bromine by treatment with phosphorus pentabromide.²²⁰ β -Bromonaphthalene may be prepared, for example, from naphthalene- β -sulfonic bromide by this treatment. Sulfones may serve in this reaction in place of the sulfonic bromides.²²¹

The action of bromine on anthracene parallels that of chlorine on this compound.

9,10-Dibromoanthracene is obtained by adding two molecular equivalents of bromine to a solution of anthracene in carbon disulfide.²²²

Bromine vapors reacting with the hydrocarbon yield the β -isomer of tetrabromoanthracene dibromide. Reaction of the halogen with anthracene in chloroform solution leads to the formation of the α -isomer of the same body. The α -isomer rapidly releases four atoms of bromine when dissolved in benzene and exposed to sunlight, and is thereby converted to 9,10-dibromoanthracene. The β -isomer remains unchanged under these conditions.²²³

1,2,9,10-Tetrabromoanthracene results on heating 9,10-dibromoanthracene tetrabromide. The tetrabromo compound is converted on oxidation to 1,2-dibromoanthraquinone.

Phenanthrene may be converted to dibromophenanthrene by subjecting the hydrocarbon to the action of bromine in glacial acetic acid solution.⁷⁴

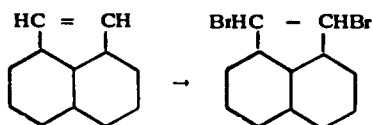
Addition of two atoms of bromine takes place when the bromination of phenanthrene is

carried out in carbon disulfide solution. The phenanthrene dibromide which results releases a molecule of hydrogen bromide and is thereby converted to 6-bromophenanthrene. Oxidation of the latter with chromic acid results in the formation of phenanthraquinone. On further bromination of the 6-bromo derivative, 4,9- or 4,10-dibromophenanthrene is obtained, which on oxidation yields 4-bromophenanthraquinone.²²⁴

Bromination of *fluorene* in boiling chloroform results in the formation of 2,7-dibromofluorene and a tribromo derivative, probably 2,6,7-tribromofluorene.²²⁵ 2-Bromofluorene is formed when the bromination is carried out in the cold.²²⁶

5-Bromo-acenaphthene is obtained by the direct bromination of *acenaphthene*.⁷³ Some tetrabromoacenaphthene is also formed in this reaction. The 3-bromo derivative is obtained from 3-aminoacenaphthene via the diazo compound.⁷⁴

Acenaphthylene adds two atoms of bromine to form a dibromide:²²⁷



The dibromide is converted to the corresponding acenaphthylene glycol when it is heated with water.

Bromination of Phenols

Bromination of phenols takes place quite readily under the action of bromine. Mono-, di-, and tribromo phenols may be obtained by the controlled action of the halogen on the phenol in solution in a suitable solvent. The element enters the *ortho* and *para* positions to the hydroxyl group. This rule holds true with respect to homologs of phenol, because the directive influence of the hydroxyl group outweighs that of the alkyl groups. Bromination proceeds readily in aqueous solution or suspension. 2,4,6-Tribromophenol is obtained when phenol is treated with bromine water.²²⁸ An excess of bromine in this reaction causes the formation of the unstable 2,4,6,6-tetrabromocyclohexadienone, also termed phenol tetrabromide. This compound readily yields an atom of bromine to unchanged phenol, and is thereby converted to tribromophenol. Dibromo derivatives are formed when phenols are brominated in organic solvents.

2,4-Dibromophenol may be obtained by adding a solution of bromine in hydrobromic acid to a cooled suspension of phenol in hydrobromic acid.²²⁹

o-Bromophenol is obtained in good yield when vapors of bromine are conducted over phenol heated at 150-180°. ²³⁰ *p*-Bromophenol has been obtained in 85% yield through the action of bromine on phenol dissolved in carbon disulfide.²³¹

The behavior of homologs of phenol, such as cresols, at room temperature, toward bromine is similar to that of phenol. The halogen enters the *ortho* and *para* positions, unless these positions are occupied by substituents. At higher temperatures or in sunlight, side-chain substitution takes place. The subject of side-chain substitution has been considered under the general heading of bromination.

3,6-Dibromo-1,2-cresol-2-methyl sulfide perbromide results when 1,2-cresol-2-methyl

sulfide is brominated in acetic acid solution; 1-4-cresol-3-sulfonic acid gives the 5-bromo derivative.³⁴⁴ Fluorescein is converted to tetrabromofluorescein (Eosin).³⁴⁵ Phloridzin has been converted to dibromophloridzin by bromination in methanolic solution; treatment of the compound with undiluted bromine causes decomposition into dextrose and tetrabromophloretin.³⁴⁶

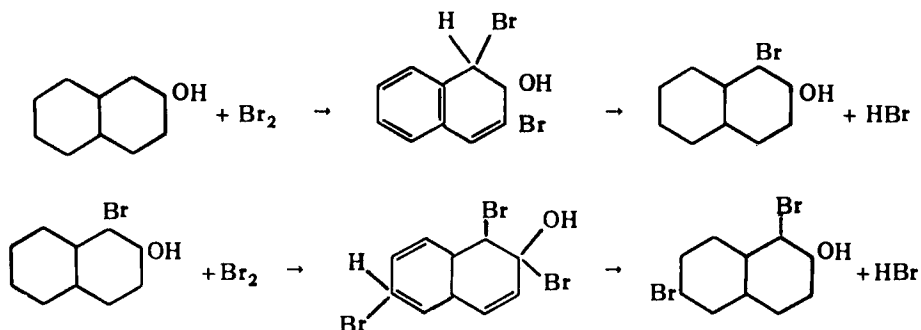
In the bromination of naphthalenesulfonic acids, removal of the sulfonic group is usually accompanied by quinone formation.

Sulfanilic acid may be brominated without removal of the sulfonic group.³⁴⁷ At temperatures above 20° the compound is converted by excess bromine to tribromoaniline.³⁴⁸ The bromination of metanilic acid may be arrested at the tribromo stage by carrying out the reaction at room temperature.³⁴⁹

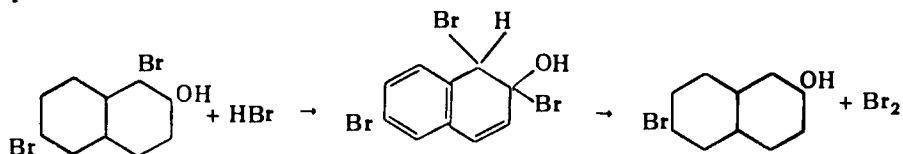
1-Naphthylamine-4-sulfonic acid yields 2,4-dibromonaphthylamine, with loss of the sulfonic group. The 5- and 8-sulfonic acids also yield 2,4-dibromo derivatives without removal of the sulfonic groups.³⁵⁰ 2-Naphthylamine-3,6- and 6,8-disulfonic acids yield dibromoderivatives with loss of one sulfo group.

Nascent bromine may act as an oxidizing agent toward phenolic bodies. Hydroquinone and pyrocatechol are oxidized when subjected to its action, but meta dihydroxybenzene is simply brominated.

In the bromination of β -naphthol, the halogen successively enters positions 1, 6, and 3.⁸⁵ On further bromination, the 1,3,4,6-tetrabromo product is formed. The course of bromination is largely influenced by the tendency of the β -naphthol molecule to assume the quinoidal form through the addition of two atoms of bromine:²³²

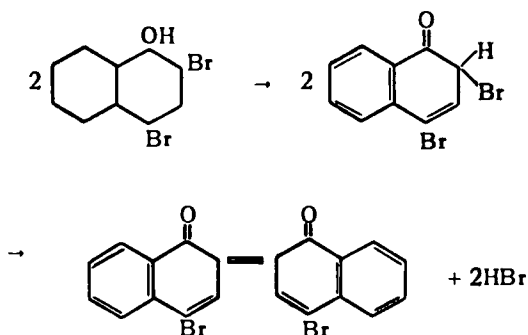


Hydrobromic acid may also add to the naphthalene molecule to yield a quinoid product. Such an addition, followed by the elimination of a molecule of bromine would explain the formation of 6-bromo- β -naphthol from the 1,6-dibromo product:



Bromination of α -naphthol leads to the formation of a 2,4-dibromo substitution product. The tendency toward the formation of quinoid type of compounds is

shown also by α -naphthol. The formation of indigotin type of derivatives from 2,4-dibromo- α -naphthol may be explained by assuming the intermediate appearance of a quinoid form:²³³



6-Bromo-2-naphthol is obtained from 1,6-dibromo-2-naphthol by reduction with tin and glacial acetic acid, or with concentrated hydriodic acid.²³⁴

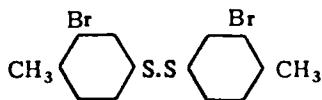
The formation of keto dibromides from 1-bromo- β -naphthol is favored by the presence of sodium acetate, which serves to remove the hydrobromic acid. Further bromination of the keto dibromide and subsequent reduction of the product yields the 1,3,6-tribromo derivative, while direct bromination gives the 1,4,6-derivative.

Bromination of 1,5-dihydroxynaphthalene leads to the formation of the 2,6-dibromo derivative, which on oxidation affords 2,6-dibromo-5-hydroxy-1,4-naphthoquinone.²³⁵

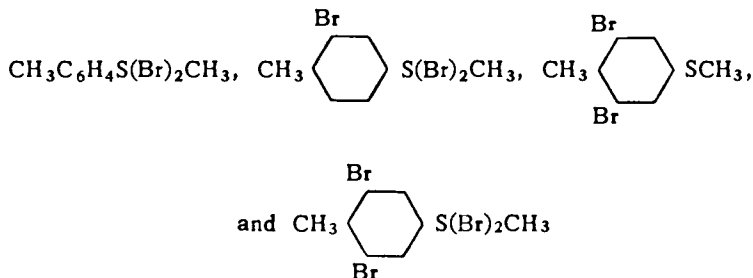
Phenolphthalein, in solution in four parts of alcohol, treated at boiling temperature with a solution of two parts bromine in two of acetic acid, gives tetrabromophenolphthalein.²³⁶

9-Hydroxyphenanthrene is best brominated to 3,10-dibromo-9-hydroxy, or 3,9-dibromo-10-hydroxyphenanthrene in carbon disulfide solution.²³⁷ A far less pure product is obtained when the bromination is carried out in carbon tetrachloride solution.

p-Thiocresol methyl ether, $\text{CH}_3\text{C}_6\text{H}_4\text{SCH}_3$, brominated in the absence of a solvent, gives the dibromodisulfide,



while on bromination in solution in carbon tetrachloride, a mixture of the following substances is obtained:²³⁸



Bromination of Quinones

Brominated quinones may be prepared, in general, by the methods employed for the preparation of chloroquinones. Direct bromination of quinone, like the direct chlorination of the compound, first results in the formation of addition compounds, which rearrange to halogenated hydroquinones, and these are finally converted to the corresponding quinones by oxidation. Hydrogen bromide, like hydrogen chloride, reacts additively with quinones or haloquinones, giving halo-hydroquinones, oxidation of which results in the formation of the corresponding quinones. It is possible, therefore, to prepare an entire series of brominated quinones from quinone, by reaction with hydrogen bromide, followed by oxidation, and repeating this succession of reactions. Hydrogen bromide, however, unlike hydrogen chloride, gives with quinone both a mono- and dibromohydroquinone;²³⁹ for this reason, the preparation of monobromoquinone in the pure form is difficult.

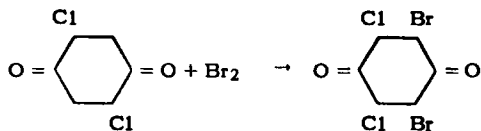
2,6-Dibromoquinone is formed by heating bromotribromophenol with lead acetate and glacial acetic acid at 60-70°. ²⁴⁰

Tribromoquinone is best obtained by heating hydroquinone with three equivalents of bromine and subsequently oxidizing the product with ferric chloride. ²⁴¹

Bromanil may be prepared from phenol by a method similar to that employed for the preparation of chloranil. The compound is best prepared, however, by brominating *p*-phenylenediamine in glacial acetic acid solution, and oxidizing the resulting product with nitric acid. ²⁴² Bromoanilic acid is obtained by heating bromanil with caustic and precipitating with hydrochloric acid. ²⁴²

p-Chlorobromoquinone is obtained by heating monochloroquinone with hydrogen bromide and oxidizing the product with ferric chloride. ²⁴⁰

m-Dichloro-*m*-dibromoquinone is obtained by brominating *m*-dichloroquinone. ²⁴³ The compound is obtained by brominating *p*-dichloroquinone in hot acetic acid solution, migration of a chlorine atom taking place during the reaction:



Migration takes place in the warm; bromination in the cold results in the formation of *p*-dichlorodibromoquinone.

Bromination of *anthraquinone* proceeds with some difficulty, though the compound may be successfully brominated at a low temperature in fuming sulfuric acid. Reaction begins at 20° with a considerable rise in temperature. When bromination is carried out in this medium at 50 to 60°, heptabromoanthraquinone is obtained as the final product. At still higher temperatures and with an excess of bromine, breakdown of the anthraquinone molecule takes place with formation of perbromobenzoylbenzoic acid, tetrabromophthalic acid, and hexabromobenzene. ²⁴⁴

While anthraquinone itself is brominated with difficulty, hydroxy- and amino-anthraquinones are brominated readily. Hydroxyanthraquinones, such as 2-hydroxyanthraquinone ²⁴⁵ and anthraflavic acid and flavopurpurin have been suc-

cessfully brominated in suspension in acid in the cold, forming respectively β,β -dibromo-2-hydroxyanthraquinone, tribromoanthraflavic acid, and di- and tribromoflavopurpurin. *p*-Bromoerythrohydroxyanthraquinone has been made by brominating erythrohydroxyanthraquinone in boiling acetic acid solution;²⁴⁶ tribromoflavopurpurin has been obtained similarly from flavopurpurin by bromination in boiling glacial acetic acid.²⁴⁷ Some hydroxyanthraquinones have been brominated in the absence of any solvent. Thus, chrysazin has been converted to dibromochrysazin rapidly when mixed with bromine, and to tetrabromochrysazin by heating with bromine in a sealed tube at 150° for an hour.²⁴⁸ Hystazarin has been converted to dibromohystazin similarly by treatment with bromine. 1-Aminoanthraquinone has been brominated smoothly in glacial acetic acid to 1-amino-2,4-dibromoanthraquinone. 1,3-Dibromoanthraquinone has been obtained from 1-amino- and 2-aminoanthraquinone by energetic bromination followed by deamination of the brominated derivative.²⁴⁹

Bromo Aldehydes

Benzaldehyde has been converted to *m*-bromobenzaldehyde by bromination in the presence of zinc chloride.²⁵⁰ While the bromination of *p*-hydroxybenzaldehyde in aqueous solution results in the formation of the 3,5-dibromo compound, the 3-bromo product may be obtained by carrying out the reaction in chloroform solution.²⁵¹

Bromination of Carboxylic Acids

It has been pointed out that halogenation of aromatic carboxylic acids proceeds with difficulty, usually requiring treatment with the halogen in a sealed tube at an elevated temperature. The first halogen enters the meta position to the hydroxyl group. Many acids have been brominated in solution under atmospheric pressure.

Anthranilic acid dissolved in dilute hydrochloric acid has been converted to 3,5-dibromoanthranilic acid in 92% yield by treatment with vapors of bromine for a period of 8 to 10 hours.²⁵² Dibromoanthranilic acid has been converted to tribromobenzoic acid by the action of bromine in hydrobromic acid solution on the diazo compound of the dibromo acid in the presence of copper.²⁵²

m-Hydroxybenzoic acid in solution in acetic acid has been converted to 4-bromo-*m*-hydroxybenzoic acid.²⁵³ Substituted *m*-hydroxybenzoic acids may also be similarly brominated. These compounds yield tribromo derivatives on further bromination if the substituent is in *meta* position. Dibromo derivatives are formed if the substituents occupy the ortho or para position, unless the substituents are readily detachable negative groups, such as COOH or SO₃H, when tribromo derivatives are obtained.²⁵⁴

o-Bromo-*p*-toluic acid has been converted to 2,5-dibromotoluic acid by heating its aqueous solution with bromine in a sealed tube at 90-95°.²⁵⁵ *Ortho* and *para* benzoic acids have been converted to more highly brominated acids by a similar treatment.²⁵⁶

Para and *meta* toluic acids brominated in hot bromoform solution give the corresponding α -bromo acids.²⁵⁷

Anthranilic acid has been brominated in aqueous solution by use of bromide-bromate mixture.²⁵⁸

Benzyl cyanide, heated to 170° and treated with bromine, gives dicyanostilbene, $C_6H_5C(CN) = C(CN)C_6H_5$.

Bromination of Aromatic Amines

The conditions to be satisfied for the successful halogenation of amines have been discussed in the section dealing with chlorinated aromatic compounds. Halogenation, as has been pointed out, proceeds with great rapidity, and the isolation of the lower substitution products is often impossible. Amines may be brominated in acid solution, or in the form of their acylated derivatives, and again, as their condensation products with aldehydes. Sulfur has proved to be a satisfactory catalyst in the bromination of aromatic amines.²⁵⁹ Substituents in the aromatic nucleus are occasionally replaced during bromination.

Anthranilic acid may be successfully brominated in acid solution. Monobromoarsanilic acid has been obtained in the pure form by brominating arsanilic acid in acetic acid solution with half the theoretically required amount of the halogen.²⁶⁰

Dimethylaniline, brominated in acetic acid solution, yields 2,4,6-tribromomethylaniline, with loss of one methyl group.²⁶¹

Acylated amines lend themselves well for the preparation of brominated amines. *p*-Bromoacetanilide has been obtained in excellent yield by carefully adding the theoretical quantity of the halogen to the solution of acetanilide in glacial acetic acid. Acetyl-aminoacetophenone, $\text{CH}_3\text{COC}_6\text{H}_4\text{NHCOCH}_3$, brominated in chloroform or sulfuric acid solution, or subjected to the action of vapors of the halogen, gives acetyl-amino- ω -dibromoacetophenone, $\text{Br}_2\text{CHCOC}_6\text{H}_4\text{NHCOCH}_3$.²⁶²

Examples of the use of aldehyde addition products are offered by the preparation of *p*-bromoaniline,²⁶³ and of brominated naphthylamines.²⁶⁴ The benzal derivatives of these amines add two atoms of bromine to form dibromides:

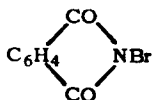


The dibromides undergo rearrangement forming nucleary brominated derivatives when their solutions are boiled, or when they are treated with pyridine. By repeating the cycle of operations with the resulting benzal derivatives of the bromoamines, additional bromine atoms may be introduced in the nucleus. In this manner, two bromine atoms have been introduced in α -naphthylamine, and three in β -naphthylamine.

N-Bromoamides

N-Bromoacetanilide, $\text{CH}_3\text{CONBrC}_6\text{H}_5$, is obtained on adding a saturated solution of boric acid to a solution of acetamide, $\text{CH}_3\text{CONHC}_6\text{H}_5$, in aqueous sodium hypobromite.²⁶⁵ The compound changes within a few hours to acetparabromoanilide in the presence of moisture.

N-Bromophthalimide,



is obtained by adding bromine water in slight excess over that required theoretically to an approximately 30% aqueous solution of sodium phthalimide.²⁶⁶ The compound is best prepared, however, by suspending 147 parts of phthalimide in a mixture of 100 parts

water and 60 parts acetic acid, and adding an equivalent of sodium hypobromite solution.²⁶⁷

Replacement of Nitro or Nitroso Groups with Bromine

Nitro or nitroso groups in aromatic compounds are, in certain instances, replaceable with bromine. The nitro group in bromonitrobenzene, for example, may be replaced with bromine by heating the compound with the halogen in a sealed tube at 75 to 80° in the presence of ferric chloride.²⁶⁸ The nitroso group in 4-nitrosophenol is replaced with bromine by subjecting the compound in alcoholic solution to the action of excess bromine.²⁶⁹

Bromination of Sulfonic Acids

Bromination of aromatic sulfonic acids may result in the formation of bromo sulfonic acids and aryl bromides, or a mixture of both types of compounds. The presence of a hydroxy or an amino group favors the replacement of the sulfonic group with the halogen. Replacement has also been observed with polyalkylbenzene derivatives.

Replacement of the sulfonic group with bromine takes place to a large extent with *meta* and *para* *cymenesulfonic acids* when these compounds are brominated at 40° in hydrobromic acid.³⁵¹ The corresponding bromopseudocumenes result when 1,2,4-trimethylbenzene-5- and -6-sulfonic acids are heated on the steam bath with bromine.³⁵² Heating with an excess of bromine results in the formation of 2,4,6-tribromomesitylene.

α-Naphthalenesulfonic acid gives a mixture of 1,5-dibromonaphthalene and 5-bromonaphthalenesulfonic acid when it is brominated in aqueous solution.³⁵³ The sulfonic group in 4-chloro and 4-bromonaphthalene-1-sulfonic acid is replaced with halogen on bromination.³⁵⁴

Phenanthrene-3-sulfonic acid undergoes bromination readily in aqueous solution, the halogen entering the 9- or 10- position.

Sulfonic groups in *ortho* or *para* position in *phenols* are replaceable with bromine, but bromination may be effected without loss of the sulfonic groups.³⁵⁵ All sulfonic groups are replaced when an excess of bromine is used.³⁵⁶ Cresolsulfonic acids behave in a comparable manner. Dihydroxybenzenesulfonic acids are very reactive toward bromine.³⁵⁷

The sulfonic group in sulfonated ethers of phenol is replaced before substitution in *ortho* position takes place.³⁵⁸

Behavior of Brominated Compounds

The behavior of aromatic bromine compounds parallels that of chlorinated compounds, a subject which has been considered in the section dealing with aromatic chlorinated compounds. Bromine compounds are, in general, more reactive and the halogen is more readily replaced than chlorine. The greater reactivity of bromine makes possible exchange reactions that cannot be carried out with the corresponding chloro compound. When bromobenzene is heated with a methyl alcoholic solution of sodium methylate at 220° in an autoclave, anisol and phenol are formed, although the reaction does not proceed readily.²⁷⁰ The bromine in *p*-bromobenzenesulfonic acid may be replaced with hydrogen by heating the alkaline solution of the compound at 100° with hydrogen under 10 atmospheres pressure in the presence of a nickel catalyst.²⁷¹

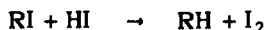
AROMATIC COMPOUNDS

AROMATIC IODINE COMPOUNDS

Methods of Iodination

Iodination with Elemental Iodine

The direct iodination of aromatic compounds cannot proceed to completion unless the hydriodic acid formed in the reaction is oxidized to iodine, or is fixed by a base. The acid, if not destroyed or bound, tends to reduce the iodo compound formed to the original aromatic body,



and the reaction proceeds to a point of equilibrium.

Iodination usually proceeds in a satisfactory manner when it is carried out in the presence of an effective oxidizing agent. The reagents commonly employed are nitric acid,²⁷² iodic acid,²⁷³ sodium persulfate,²⁷⁴ mercuric oxide,²⁷⁵ lead oxide, and silver oxide.

Iodination may be effected satisfactorily by mixing the substance to be iodinated with an equal weight of iodine and adding an equal amount of 70% nitric acid in small portions. The mixture should be kept cool during the addition of the acid, and then slowly warmed, finally heating it on a sand bath for a few hours.

Nitric acid may cause nitration of the aromatic compound in this reaction. In the iodination of benzene by this method, only a very small amount of trinitrophenol is formed, while naphthalene gives very appreciable quantities of nitronaphthalene. Anthracene is oxidized to anthraquinone when subjected to the simultaneous action of iodine and nitric acid.²⁷⁶

Iodination may be carried out in solution in various solvents,²⁷⁷ such as alcohol, acetone, ether, petroleum ether, benzene, chloroform, carbon disulfide, and glacial acetic acid. Methyl alcohol is more resistant to the action of iodine than ethyl alcohol, and is, therefore, a more satisfactory solvent than the latter for iodination reactions.²⁷⁸ The reaction may be carried out also in aqueous potassium iodide, alkalies, or borax.

Fuming sulfuric acid has also been employed for the purpose of oxidizing hydriodic acid generated in the course of iodination reactions. Sulfuric acid of 50% anhydride content is generally used; it is made by melting 100 parts of commercial pyrosulfuric acid of 80% anhydride content and adding 55 parts of concentrated sulfuric acid.²⁷⁹ Fuming sulfuric acid has also been used in conjunction with sodium nitrite as an oxidizing agent in the iodination of aromatic compounds.²⁸⁰

Basic substances have been employed to carry out iodination reactions. Ammonium hydroxide has been used for this purpose with satisfactory results. Phenolic bodies have been iodinated by its use.²⁸¹

The procedure is to dissolve the phenol in concentrated ammonia, and to add iodine to the solution until the color of the halogen persists. The iodo compound separates as a solid.

Nitrogen iodide would appear to be the actual iodinating agent in this reaction.

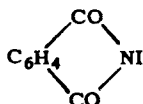
Caustic soda has also been used in iodination reactions. The role of this base would appear to be that of forming sodium hypoiodite and iodate by reaction with iodine, rather than of acting as an acid binding agent to fix the hydriodic acid formed by the direct reaction of the halogen with the aromatic body.²⁸²

Triiodophenol has been obtained by the reaction of iodine with potassium phenolate in aqueous solution containing an excess of three equivalents of potassium hydroxide.²⁸³

Aromatic amines in solution in acetic acid are directly iodinated by reaction with the halogen because of the binding power of the base for hydriodic acid. Aromatic amines have also been effectively iodinated in the presence of calcium carbonate.

Phenolphthalein has been converted to the triiodide by treatment with iodine in solution in aqueous potassium iodide in the presence of borates.²⁸⁴ This method offers the advantage that the iodo compounds formed may be readily purified.

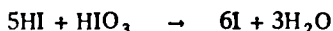
Iodoformanilide, $C_6H_5NICH_3$, has been obtained from the silver derivative of form-anilide by exchange of the metal with iodine by reaction with the element.²⁸⁵ N-Iodophthalimide,



has been obtained by the action of iodine on sodium phthalimide.²⁸⁶ Since the sodium iodide formed combines with the iodophthalimide, it must be eliminated by carrying out the reaction in the presence of bromine or chlorine.

Use of Nascent Iodine

Iodination of organic bodies may be carried out by use of nascent iodine. This method makes possible the complete utilization of the available iodine. Several methods are employed for the generation of nascent iodine. In one method, iodic acid is employed as the oxidizing agent to generate the halogen:



The procedure is to acidify the solution of the organic body with sulfuric acid and to add the calculated amount of the iodide-iodate mixture. A five to two molecular ratio of the iodide to iodate must be employed in order to bring about complete utilization of the iodine, this ratio holding for the mono iodination of six molecular proportions of the aromatic compound. Acetic acid may be used instead of sulfuric acid for the liberation of iodic acid and hydrogen iodide.

Another method employed for the generation of nascent iodine is to dissolve the element in aqueous caustic and then to acidify the solution. Iodine may be generated also by the interaction of potassium iodide and chloride of lime in aqueous solution at boiling temperature. The reaction of sulfur moniodide with nitric acid of specific gravity 1.2 has also been utilized for the generation of iodine.²⁸⁷ This method is especially suited for the iodination of alkyl aromatic

compounds, which are nuclearly iodinated to monoiodo derivatives, the side-chain remaining unattacked.

Excess iodine remaining after completion of an iodination reaction may be removed by distillation with steam; or the element may be eliminated by adding sulfurous acids, sodium thiosulfate, or alkalies. Hydrogen sulfide may also be used for the purpose. The iodine may be removed, finally, by shaking the reaction mixture with metallic mercury.

Use of Iodinating Agents

Iodination of aromatic compounds may be accomplished by use of iodinating agents, i.e., compounds which readily yield their iodine. Outstanding among such compounds is iodine chloride, ICl . Iodine trichloride, ICl_3 , and hypiodous acid are other examples of iodinating agents. Iodine monochloride is particularly well suited for the iodination of amino compounds and certain phenolic derivatives.

Iodine monochloride may be prepared by conducting a current of dry chlorine over iodine until somewhat less than the theoretically calculated amount of chlorine is absorbed.²⁸⁸ The molecular compound of iodine monochloride and hydrochloric acid, $\text{ICl}\cdot\text{HCl}$, has also been used as an iodinating agent. This compound may be prepared more readily than iodine monochloride; it is formed when sodium nitrite is added gradually to a mixture of iodine and hydrochloric acid.²⁸⁹

Iodo compounds may be prepared readily by replacement of the *diazo* group in an aromatic diazo compound by boiling the iodide of the diazo body with hydriodic acid.²⁹⁰ This offers a satisfactory method for the preparation of aromatic iodides if the required amino compound is readily accessible. 2-Aminofluorene has been converted by this method to 2-iodofluorene.²⁹⁴

Iodination of Various Types of Compounds

Iodination of Aromatic Hydrocarbons

Aromatic hydrocarbons may be iodinated by iodine in the presence of the appropriate oxidizing agent.

Benzene has been converted to iodobenzene in 75 to 80% yield by treatment with iodine in the presence of nitric acid. Iodobenzene subjected to the same treatment gives *p*-diiodobenzene; toluene yields *o*- and *p*-iodotoluenes; *o*-xylene gives 4-iodo-*o*-xylene, and *m*-xylene affords 4-iodo-*m*-xylene. The iodination of benzene and its homologs also proceeds smoothly in the presence of sodium persulfate.²⁷⁴ The hydrocarbon may be iodinated effectively at 200–240° with a mixture of iodine and iodic acid.²⁰⁹ Homologs of benzene are iodinated more readily by this treatment.²⁹¹ *Mesitylene* has been converted to moniodomesitylene by use of iodine and mercuric oxide.²⁹² Durol is converted to moniododuroil by this treatment.

Naphthalene may be iodinated by heating with a mixture of iodine and nitric acid.²⁷² α -Iodonaphthalene is obtained as the main product of the reaction, accompanied by a small amount of the β -iodo derivative.

Acenaphthene is converted to moniodoacenaphthene when treated with iodine and mercuric oxide.²⁹³

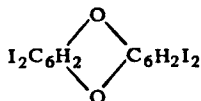
Iodination of Phenols

Iodine in aqueous potassium iodide solution reacts with sodium phenolates in dilute alkaline solution.²⁹⁵ Phenol gives triiodophenol, and cresol triiodocresol. The reaction proceeds quantitatively under the proper conditions, and may be employed for the determination of phenols and β -naphthols.

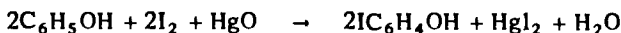
Flocculent, colored precipitates have been obtained by the action of iodine in aqueous potassium iodide on alkaline solutions of phenols. These are apparently addition compounds which yield their halogen readily and may be successfully substituted for iodoform in its pharmaceutical uses. They have the advantage that they are devoid of odor. Among the more important products of this type are *aristol*, a derivative of thymol, and *Europen*, a derivative of isobutyl-*o*-cresol.²⁹⁶

Salicylic acid in aqueous ammoniacal solution, treated with less than a molecular proportion of iodine dissolved in aqueous sodium iodide, is converted to 5-iodo-2-hydroxybenzoic acid and isomeric products.²⁹⁷

It has been claimed that iodine in excess, reacting with phenol, salicylic acid, or *p*-hydroxybenzoic acid, in the presence of alkalis or alkali carbonates gives tetraiododiphenylene dioxide.²⁹⁸

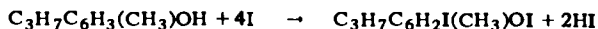


Iodination of phenol to monoiodophenol has been effected by reaction with iodine in alcoholic solution in the presence of mercuric oxide.²⁹⁹ The reaction proceeds vigorously at ordinary temperature:

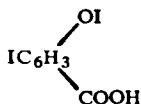


Iodine and concentrated nitric acid, reacting with phenol, give 2,4-dinitro-6-iodophenol.³⁰⁰

Iodination of phenols may be accomplished by use of nascent iodine and results in the replacement of the phenolic hydroxyl group with iodine, as well as substitution of nuclear hydrogen atoms.³⁰¹ Iodothymol iodide is obtained from thymol by the action of nascent iodine generated from hypoiodite, or with potassium iodide and chlorine, and other reagents:



Iodosalicylic acid iodide,



has been prepared by this method from salicylic acid.³⁰²

Phenols may be iodinated satisfactorily by the action of iodine in the presence of ammonia.³⁰³ The active agent in this reaction would appear to be nitrogen triiodide, a powerful iodinating agent. Phenol gives in this reaction triiodophenol, and *o*- and *p*-cresols give diiodocresols; *o*-nitrophenol gives 2,6-diiodo-4-nitrophenol; salicylic acid gives 5-iodosalicylic acid, and *p*-hydroxy-

benzoic acid gives 3,5-diiodo-*p*-hydroxybenzoic acid. Iodothymol has been obtained by this method from thymol.³⁰³

Bromoanil reacting with sodium iodide gives dibromodiiodoquinone as the principal product, together with iodoanil and some tribromodiiodoquinone.³⁰⁴

Iodoquinones have been prepared through the oxidation of iodoaminophenols and iodo-phenylenediamines.³⁰⁵

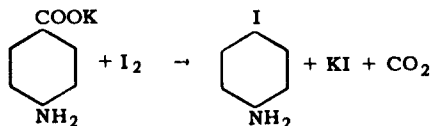
Iodinated Aromatic Acids

Benzoic acid, subjected to the simultaneous action of iodine and concentrated nitric acid, is converted to 3-iodobenzoic acid.³⁰³ Other iodinated benzoic acids may be prepared by the indirect methods of halogenation mentioned in connection with chlorinated acids.

Aromatic carboxylic acids in which an iodine group is present in the *ortho* position are, as a rule, readily converted to *iodoso acids*³⁰⁶ by treatment with fuming nitric acid or with potassium permanganate.³⁰⁷ *Meta* and *para* iodo acids are not changed by this treatment, although *p*-iodonitrobenzoic acid can be converted to the corresponding iodoso acid.³⁰⁸ The *o*-iodoso acids may also be prepared by the action of alkalis on the corresponding iodochloride, but the *m*- and *p*-iodochlorides cannot be thus converted to the iodoso acids. *o*-Iodosobenzoic acid is weaker than carbonic acid; its silver salt is explosive in the dry state. When treated with warm alkaline permanganate solution, it is partially reduced to *o*-iodobenzoic acid, and partly oxidized to *o*-iodoxybenzoic acid, $\text{HOCOC}_6\text{H}_4\text{IO}_2$.³⁰⁹ The latter may be obtained more conveniently through the action of chlorine on an alkaline solution of *o*-iodosobenzoic acid. *o*-Iodoxybenzoic acid is unstable and decomposes gradually on storage; it explodes when heated to 233° . On heating the compound with aqueous sodium hydroxide, it decomposes, giving sodium benzoate and sodium iodate. It is of a strongly acidic character.

The *meta* and *para* iodosobenzoic acids may be prepared from the corresponding iodo-chlorides by very careful decomposition with caustic, for example, by grinding the compound with very dilute sodium hydroxide solution, then neutralizing the excess of the latter. The *meta* acid decomposes rapidly at 180° , the *para* isomer at 210° .

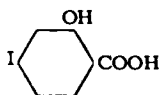
Potassium *p*-aminobenzoate in aqueous solution reacts with iodine at room temperature to form *p*-iodoaniline:³¹⁰



Similarly the potassium salt of 3,5-diiodo-4-aminobenzoic acid in aqueous solution, heated with iodine gives 2,4,6-triiodoaniline.³¹⁰

Benzoic acid has been converted to hexaiodobenzene by heating with a mixture of iodine and fuming sulfuric acid, first at 120° for half an hour, then at 180° for six hours.³¹¹

Monoiodosalicylic acid,



has been obtained in the form of its sodium salt by adding a solution of disodium salicylate to one of iodine in caustic cooled with pieces of ice.³¹² The compound may be

obtained also by the action of iodine in solution in aqueous potassium iodide on an alkaline solution of salicylic acid. Homologs of salicylic acid and salicylamide may also be iodinated by this method.

p-Aminobenzoic acid has been converted to its diiodo derivative by leading the vapors of two molecular equivalents of iodine monochloride through the solution of the amino acid in a large excess of dilute hydrochloric acid.³¹³ Iodinated aminosulfonic acids may also be prepared by this method.³¹⁴

Phthalic anhydride and phthalic acid have been converted to their tetraiodo derivatives by heating with iodine and fuming sulfuric acid first at 90 to 100°, then at 180° until the evolution of gas ceases.³¹⁵

Iodination of Aromatic Amino Compounds

Aromatic amines in acetic acid solution may be directly iodinated with elemental iodine.³¹⁶ The three isomeric toluidines may be iodinated, for example, by heating with iodine in the presence of a little ether, some water, and excess of calcium carbonate.³¹⁷ *o*-Toluidine, treated in this manner, gives a monoiodo derivative, *p*-toluidine a mono and diiodo derivative according to the quantity of iodine used, while *m*-toluidine gives a triiodo derivative.

Iodine monochloride has been employed successfully for the iodination of aromatic amino compounds. Vapors of the monochloride, diluted with air, are conducted into the solution of the amino compound in a large excess of hydrochloric acid.³¹⁸ The unsubstituted amines generally give resinous products when subjected to the action of iodine monochloride. Aniline has been successfully iodinated, however, to 2,4-diiodoaniline by treating a dilute glacial acetic acid solution of the base with two molecular equivalents of iodine monochloride;³¹⁸ triiodoaniline is obtained when three molecular equivalents of the monochloride are used. *p*-Nitraniline has been successfully iodinated by this method.³¹⁹

Behavior of Aromatic Iodo Compounds

Iodobenzene and substituted iodobenzenes have the property of adding two atoms of chlorine to form iododichlorides, RICl_2 .³²⁰ The reaction is carried out in the cold in chloroform solution, or in solution in other inert solvent. The presence of several negative groups in the aromatic nucleus prevents the reaction. Thus, *cis*-tetrachloriodobenzene and pentachloriodobenzene do not yield iododichlorides, the iodine becoming replaced with chlorine when they are treated with this element. Trichloriodobenzenes are capable of forming iododichlorides.³²¹

Aqueous alkalis convert iododichlorides into iodoso compounds:



Sodium carbonate rather than sodium hydroxide is used for preparative purposes. Iododichlorides may also be converted to iodoso compounds by adding water gradually to a pyridine solution of the iododichloride. Iodoso compounds are readily oxidized to iodoxy compounds, RIO_2 . Oxidation may be effected with aqueous hypochlorite, although the transformation may also be brought about by simple boiling with water. In the aliphatic series, this transformation takes place only with iodoso compounds in which the iodoso group is attached to a doubly bound carbon atom.

Iodoso- and iodoxybenzene yield diphenyliodonium hydroxide, $(C_6H_5)_2IOH$, when shaken with an aqueous suspension of silver oxide. Nitro-, halo-, and alkyl-substituted iodoso and iodoxy compounds also undergo this reaction. Diphenyliodonium hydroxide is strongly basic. Phenyl iododichloride reacts with mercury diphenyl to form diphenyliodonium chloride.³⁵⁹ Some unsymmetrical iodoaryl iodonium salts have been obtained from iodosobenzene and its homologs by treatment with concentrated sulfuric acid;³²²



The diacetate, $RI(OCOCH_3)_2$, is formed when an iodoso compound, RIO , is dissolved in glacial acetic acid. Other compounds of this type are formed through the reaction of the iodoso compound with organic as well as inorganic acids. Iodoso compounds containing several negative substituents in the nucleus yield basic salts.³²³

AROMATIC FLUORO COMPOUNDS

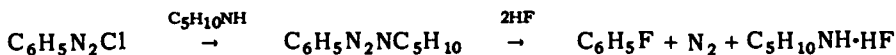
Fluorinated aromatic hydrocarbons cannot, in general, be obtained by the direct action of fluorine on the hydrocarbon.³²⁴ Aromatic fluorohydrocarbons have been prepared, however, by the action of certain metallic fluorides on the hydrocarbon at elevated temperatures. Perfluoromethylcyclohexane has been obtained in 67% yield by passing vapors of o-xylene diluted with nitrogen over heated cobalt trifluoride, CoF_3 . Perfluorotrimethylcyclohexane has been obtained similarly in 50% yield from mesitylene.³⁶⁰ Fluorinated compounds are formed in good yield by this method from trifluoromethyl derivatives of aromatic hydrocarbons. Difluorobenzoic acid has been prepared from benzoic acid by the action of chromium hydropyrufluoride.³⁶¹

Aromatic fluoro compounds may be prepared by an exchange of chlorine or bromine atoms with fluorine by reaction with salts of hydrofluoric acid, especially with silver fluoride. More often they are prepared from aromatic diazonium sulfates by heating with hydrofluoboric acid.³²⁵ A very satisfactory procedure is to precipitate the sparingly soluble diazonium borofluoride ArN_2BF_4 , and to heat the dried salt, whereupon the fluoro compound is formed:³²⁶



Control of acidity of the medium is important during the precipitation of the borofluoride. For this reason, sodium borofluoride is used as the precipitant rather than borofluoric acid, at least in the initial stages of the reaction, in order to avoid, as far as possible, the deleterious effect of the acid.³²⁷ *p*-Fluorotoluene, 4-fluoro-1,3-dimethylbenzene, α -fluoronaphthalene and 4,4'-difluorobiphenyl have been prepared by this method.

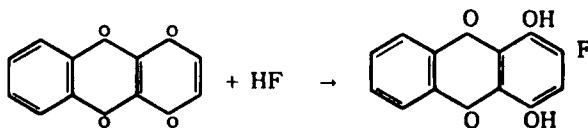
The diazo group in aromatic compounds may be replaced with fluorine by treating the compound with a mixture of piperidine and hydrogen fluoride.³⁶²



Yields are generally about 50%.

Hydrogen fluoride does not, in general, react additively with quinones. Reac-

tion takes place, however, with anthradiquinone with the formation of 2-fluoro-quinazarine in 75% yield:



Only black tarry substances are obtained from benzoquinone.³⁶³

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CHAPTER 29

AROMATIC NITRO AND NITROSO COMPOUNDS

Methods of Nitration

The basis of the process for most of the methods of nitration is the reaction of nitric acid with the substance to be nitrated. The overall reaction may be expressed by the equation:



Direct nitration with ordinary commercial nitric acid is possible in a limited number of cases; very susceptible bodies may be nitrated even with dilute nitric acid. For the nitration of the more resistant compounds, nitric acid of higher strength than the commercial product may be employed. The majority of nitration reactions are carried out, however, by use of a mixture of commercial nitric acid and concentrated sulfuric acid.

Although the *mechanism* of nitration reactions cannot be considered as fully established, there is a considerable body of evidence to show that the nitronium ion, NO_2^+ , is the actual nitrating agent.¹ Nitric acid is known to be dimolecularly associated, and evidence tends to show that the acid is, in reality, composed of a mixture of the pseudo acid, HONO_2 , incapable of dissociation, and of the true acid, HNO_3 , largely in combination with the nitronium ion and the hydroxonium ion. Nitronium ions apparently arise through the combination of the true acid with the pseudo acid:



The pseudo acid content of concentrated acid is very high, about 70% of the total acid in nitric acid of 77.3% concentration, for example. It decreases very rapidly with decrease in the concentration of the acid, and is only 2% of the total acid in nitric acid of 32% strength. The proportion of the true acid increases with increase in dilution; thus, while it forms 25% of the total acid in nitric acid of 77% concentration, the proportion rises to 60% in nitric acid of 32% strength.

The function of sulfuric acid in mixed acids appears to be that of increasing and holding at a high level the concentration of nitronium ions. An equation may, in fact, be written of a reaction between nitric acid and sulfuric acid, giving rise directly to nitronium ions:



It may be pointed out that a quantitative study of the Raman spectrum of mixtures of sulfuric and nitric acids indicates that nitric acid is totally or partially dehydrated to its anhydride,

Nitration reactions are carried out occasionally by use of oxides of nitrogen and, more frequently, in special cases, by means of alkyl nitrates, acetyl nitrate, benzoyl nitrate, etc.

Substituents in the benzene nucleus may exert a marked effect on the rate of nitration; methyl groups exert little effect, but longer alkyl chains have a greater influence. Phenols and amines are most readily nitrated, while carboxylic and sulfonic acids and nitro compounds are generally resistant to nitration. Halogenated compounds are usually nitrated with ease, though the reverse process of the halogenation of nitro compounds takes place with difficulty and requires the use of halogen carriers.

Substituents exert a directive effect on the position of entrance of the nitro groups. A nitro group already present in the benzene nucleus directs the second nitro group to the *meta* position, while a hydroxyl group has an *ortho-para* directing influence. The effect of a hydroxyl group supersedes that of a nitro group.

In the nitration of aromatic compounds with *meta* substituents, hydroxylated compounds may be formed as by-products in appreciable amounts.² The *meta* nitro derivative formed in the nitration of acetophenone is hydroxylated giving 3-nitro-4-hydroxyacetophenone.

Undesired substitution in certain positions may be prevented by protecting these positions with readily removable substituents, usually a sulfonic group, and more rarely an amino or a carboxyl group, which are eliminated after nitration.

Occasionally nitration proceeds more satisfactorily when substitution at the desired position is first effected under mild conditions with a sulfonic group, and subsequently by a nitrating agent, causing the replacement of the sulfonic group with a nitro group.

Anomalous behavior is observed in a number of instances. Contrary to Holleman's substitution rule,³ acetophenone gives on nitration *ortho* and *meta* nitro derivatives. A similar behavior is shown by benzoic acid. As a general rule, when a highly substituted benzene derivative is nitrated, the group *meta* to the first entering nitro group is replaced with a nitro group. Exceptions to this generalization, known as *Barbier's rule*, are offered by pentamethylbenzene and pentaethylbenzene, which give on nitration dinitrorethene and p-dinitrotetraethylbenzene respectively. The acetyl and benzoyl group in some highly substituted aromatic ketones are readily replaced. Abnormal behavior of this nature is shown particularly by phenolic ethers. Other instances of abnormal behavior have been discussed in connection with various types of nitrated products.

Nitration by Use of Nitric Acid

Little need be said about the use of nitric acid alone in nitration reactions. It may be pointed out that ordinary nitric acid tends to exert an oxidizing action, which increases, within limits, with increasing dilution with water.⁴ The oxidizing effect is also largely influenced by temperature, and since the nitrating power of the acid is not greatly diminished on lowering of the temperature, it is

possible, in individual cases, to carry out the nitration of a readily oxidizable substance successfully at a sufficiently low temperature.

Nitric acid is often used in solution in acetic acid. An advantage of this procedure is that it makes possible the use of the theoretically required amount of nitric acid.⁵ Carbazole has been nitrated to dinitrocarbazole by adding 1.3 parts of nitric acid of density 1.38 to a solution of 1 part carbazole in 5 parts of glacial acetic acid and heating the mixture at 100° for one hour. In those cases in which undiluted nitric acid reacts too vigorously and yields di- or polynitrated derivatives, dilution with acetic acid moderates the action of the nitric acid and makes possible the preparation of mononitro derivatives. On the other hand, the use of glacial acetic acid as a solvent weakens the nuclear nitrating tendency and accentuates the side-chain nitrating tendency of the reagent. Oxidation of the side-chain also occurs, especially upon energetic nitration. It is possible to obtain a good yield of products nitrated in the side-chain by the proper choice of the conditions.

Nitrations have also been carried out in *acetic anhydride* solution. The anhydride appears to exert a catalytic influence due to the formation of diacetyl-orthonitric acid; it also serves to eliminate the water formed in the process of nitration.⁷ Toluene in acetic anhydride solution is converted quantitatively to nitrotoluene even with the theoretical amount of nitric acid. Nitration of acetanilide in acetic anhydride solution leads to the formation of the *ortho* nitro derivatives, while nitration in sulfuric acid gives the *para* nitro derivative.⁸

Carbon tetrachloride and methylene chloride have been used as solvents in nitration reactions. Bromodurol has been converted to 3,6-nitrobromodurol by nitration in these solvents.⁹ Alcohol, acetone, ether, chloroform, benzene, nitrobenzene, and polychloroethanes have also been used as solvents in nitration reactions. The organic body, if insoluble in these solvents, may be suspended or emulsified in these liquids and subjected to the action of nitric acid.

Phosphorus pentoxide has been employed for the purpose of eliminating the water formed in the nitration reaction. Fluorobenzene has been converted to o-fluoronitrobenzene by nitration in the presence of phosphorus pentoxide.¹⁰

Certain aromatic bodies are not nitrated readily by the action of ordinary commercial nitric acid. In such cases nitric acid of higher strength or red fuming nitric acid may effect the nitration successfully. Anhydrous nitric acid has been used as a nitrating agent in carbon tetrachloride or chloroform solution.¹¹ Nitration with fuming acid at -11 to 0° favors the formation of nitrates. Nitrate formation takes place more readily with poly-substituted benzenes.¹²

Anhydrous nitric acid is made by adding nitrogen pentoxide to nearly anhydrous nitric acid, somewhat in excess over the quantity required to produce anhydrous acid; the excess of pentoxide is determined analytically by titration, and the calculated quantity of nitric acid of known water content is introduced to convert the excess of pentoxide to nitric acid.¹³ Nearly pure nitric acid may be prepared by mixing commercial concentrated nitric acid with two volumes of concentrated sulfuric acid with ice cooling, and distilling the mixture under vacuum in an all-glass apparatus. On repetition of the treatment with concentrated sulfuric acid and distillation, an acid of satisfactory purity is obtained. The liquid must be cooled to -20° during the second treatment with sulfuric

acid, and the receiver should be cooled with a mixture of ether and solid carbon dioxide during the final distillation.¹⁴ Nitric anhydride is made by adding commercial pure nitric acid hydrate to twice its weight of phosphorus pentoxide, and distilling the anhydride, which deposits as a solid on the walls of the receiver. The yield of anhydride is about 70%.¹⁵

Red fuming nitric acid is prepared by mixing 100 parts by weight of concentrated sulfuric acid and 3 to 5 parts of starch with 100 parts of sodium nitrate, and condensing and collecting the vapors which are generated. The distillation is completed by gently warming toward the end.¹⁶

Nitration reactions are also carried out by use of mixtures of acetic anhydride and metallic nitrates. Satisfactory nitrates are those of copper, iron, manganese, cobalt, nickel, mercury, silver, sodium, and lithium.¹⁷ Such mixtures react in the same manner as acetyl nitrate; they bring about nitration at low temperatures, and yield principally *o*-nitrated products. *p*-Nitrated products are obtained when nitration is carried out at a higher temperature by use of lithium nitrate. By making use of this method, the formation of resinous products may be avoided.

Nitrous acid exerts a marked effect in nitration reactions. Since this acid is itself a strong nitrating agent, it enhances the nitrating power of nitric acid. Certain compounds, such as phenols, are readily nitrated with nitric acid containing a little nitrous acid, but are not attacked in ethereal solution by nitric acid entirely free from nitrous acid.¹⁴ Since hydrazine has the power to combine with nitrous acid, the addition of a small amount of this compound to nitric acid may prevent its reaction with phenols. Nitration of phenols in alcoholic solution with nitric acid proceeds readily because of the formation of nitrous acid through the reaction of alcohol with nitric acid.¹⁸

The presence of nitrous acid in nitric acid is undesirable when carrying out the nitration of amines, and the compound is therefore carefully eliminated from acid used for this purpose.

The preparation of nitric acid entirely free from nitrous acid is not a simple matter. Distillation under 20 to 30 mm pressure usually gives an acid containing less than 0.1% nitrous acid. A more complete purification is possible by distilling nitric acid to which some urea has been added. Approximately 1.3 gm of urea should be added to every gram of nitrous acid present in the nitric acid; 1.7 to 2.0 gm of urea per 100 gm of nitric acid are usually sufficient. The nitrous acid content of the acid may be reduced by this method to about 0.05%.

An alternative method is to add 6 gm of urea per 1000 cc of nitric acid, to boil the acid and sweep out the nitrous gases by a current of air or carbon dioxide.¹⁹ It is often possible to destroy the nitrous acid directly in the reaction mixture by the addition of urea.

The degree of nitration of a compound is dependent on the concentration of the acid employed, its amount, and the temperature. The effect of temperature is especially marked, and it is often possible to stop the nitration largely at the desired point by controlling the temperature of the reaction.

Nitration by Use of "Mixed Acids"

Many aromatic compounds which are not successfully nitrated with nitric acid, readily undergo nitration under the action of a mixture of nitric acid with con-

centrated sulfuric acid, usually referred to as "*mixed acids*." The function of sulfuric acid is not solely that of eliminating the water formed in the reaction; it combines with nitric acid, a fact that is clearly indicated by the considerable heat evolved on mixing the two acids.²⁰ As has been pointed out previously, this fact is responsible for a rise in the concentration of the nitronium ion, considered to be the actual nitrating agent. In many cases sulfuric acid performs a further important function, that of a common solvent for the substance to be nitrated and the nitrating agent. The high boiling point of the acid mixture is also a distinct advantage in many instances. The use of mixed acids suppresses side reactions caused by nitrogen oxides. It should be noted that sulfuric acid often exerts a directive influence on the position of entrance of the nitro group.²¹

The usual *procedure* followed in preparing a mononitrated aromatic hydrocarbon is to mix concentrated sulfuric acid with an equal volume of 70% nitric acid, and to run the compound to be nitrated into the mixture held below 50°. The amount of mixed acids used should be about 5% in excess over the theoretically required quantity. It is customary to complete the reaction by heating the mixture on the water bath for a short period. The whole is finally cooled, the acid layer is separated from the organic layer, and the latter is washed, dried, and purified by distillation. The course of nitration may be followed by determining the nitric acid content of the reaction mixture by measuring the electrode potential of the solution by use of a platinum electrode.²²

The speed of nitration is proportional to the concentration of both the nitric acid and the aromatic compound, and also depends on the composition of the medium, reaching a maximum usually in a mixed acid prepared with 90% sulfuric acid.

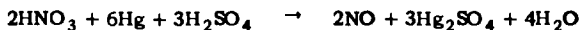
If a dinitro compound is to be prepared, the amount of mixed acid used is doubled.²¹ It is also advisable to use fuming or 90% nitric acid in making the nitrating mixture. In order to achieve a still higher degree of nitration, it is necessary to use nitric acid of the highest concentration, and to replace a portion of the concentrated sulfuric acid with fuming sulfuric acid. In many cases water bath temperatures are not sufficient to bring about a high degree of nitration, and the reaction mixture must be heated at 130°. Good agitation and heating for a long period may be necessary in nitrating resistant substances insoluble in the mixed acids.

It is desirable to carry out the nitration in stages when preparing trinitro compounds, first making the mononitro product by use of a weaker acid mixture, then nitrating this further by means of a stronger mixed acid at a higher temperature. This procedure is often of advantage even in preparing dinitro compounds.

In certain cases a mixture of nitric acid and fuming sulfuric acid is used as a nitrating agent. This mixture is employed, for example, for the nitration of terephthalic acid, which is hardly attacked at all by ordinary mixed acids.²³ Mixtures of concentrated sulfuric acid and a metal nitrate, such as nitrates of potassium, copper, nickel and cobalt, have also been used as nitrating agents. Drastic nitration by such mixtures is possible by heating in a sealed tube. *p*-Nitroquinoline, which cannot be nitrated further by the usual methods, has been converted to dinitroquinolines by this treatment.²⁴ Pyridine, which is also very resistant to nitrating agents, has been converted to β -nitropyridine by this method, although the yields are very poor.²⁵ Halopyridines give halonitropyridines in considerably better yield.²⁶

Aromatic hydrocarbons have been nitrated by electrolysis in methanolic solutions of nitric acid.²⁷

The extent of nitration in a nitration reaction may be determined by estimating the nitric acid content of the reaction mixture at any given stage. This can be done by converting the nitric acid present in the liquid into nitric oxide by reaction with metallic mercury and sulfuric acid:



The nitric acid can be estimated by measuring the volume of the nitric oxide formed by use of the Lunge nitrometer. The degree of nitration may then be calculated from the known initial concentration of nitric acid in the nitrating acid.

Use of Nitrosylsulfuric Acid

Nitrosylsulfuric acid, HOSO_2NO_2 , acts as a powerful nitrating agent at 20-30°. Aromatic hydrocarbons are readily nitrated by this compound, and halo benzenes are converted to their *p*-nitroderivatives. Benzoic acid yields *m*-nitrobenzoic acid when treated with this reagent, but aniline is decomposed and charred.²⁸ Nitrosylsulfuric acid is best obtained by passing sulfur dioxide into nitric acid maintained at room temperature, until half the theoretically required quantity of the dioxide has been absorbed.²⁹ The nitric acid solution of the compound thus obtained usually contains 40-50% nitrosylsulfuric acid, and can be used directly in nitration reactions at 30°. The mixture is a more vigorous nitrating agent than mixed acids.

Use of Nitrous Acid

Nitrous acid may act as a nitrating agent, and is suitable for the nitration of certain classes of compounds. Phenanthrene, chloranil, and salicylic acid have been nitrated by its use. The acid may be generated in the reaction mixture from a metal nitrite and sulfuric acid. The acid is readily obtained in the liquid state by heating nitric acid with arsenious oxide and condensing the vapors evolved in a well cooled receiver. The liquid boils at 30°. The acid may also be generated by heating nitric acid with starch.³⁰

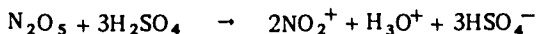
In *Fredenhagen's process*, powdered sodium nitrite is added to a mixture of the aromatic body with anhydrous hydrogen fluoride. Mesitylene has been converted by this method to dinitromesitylene in 94 to 98% yield by carrying out the reaction at a temperature below 5°. ³⁸⁹

Nitration by Use of Oxides of Nitrogen³¹

Nitrogen tetroxide, N_2O_4 , of itself, shows little activity toward benzene, chlorobenzene, toluene and naphthalene in ethereal solution. The ability of aromatic compounds to react with this oxide increases with increasing substitution.³² Naphthalene is readily acted upon by nitrogen tetroxide, forming first an addition product, which soon decomposes to α -nitronaphthalene and nitrous acid.³³ Reaction fails to proceed in ethereal solution, however, apparently because of the formation of an addition compound between ether and the oxide. The nitrating action of nitrogen tetroxide is greatly enhanced in the presence of strong sulfuric acid.³⁴ Benzene and toluene have been nitrated successfully by a mixture of the oxide with sulfuric acid, with yields approximating 90% of the theoretical. A mixture of nitrogen oxides and aluminum nitrate have been used

for the nitration of hydrocarbons.³⁵ Nitrogen tetroxide may be prepared by heating nitric acid of density 1.38 with arsenious oxide, and saturating the resulting gas with oxygen.³⁶

Nitric anhydride, N_2O_5 , is a vigorous nitrating agent, and reacts readily with aromatic compounds in the absence of sulfuric acid or aluminum chloride. Sulfuric acid enhances the nitrating action of the compound by virtue of its ability to produce nitronium ions according to the equation:



Carbon tetrachloride appears to be the most satisfactory solvent for the compound.

Nitric anhydride may be prepared by mixing anhydrous, or nearly anhydrous nitric acid with twice its weight of phosphorus pentoxide. On shaking the slightly warmed mixture, the anhydride distills over and collects as a solid in the receiver. The anhydride may be obtained by this method in yields of about 70% of theory.³⁷

Nitration with Other Nitrating Agents

Acetyl nitrate, $\text{CH}_3\text{COONO}_2$, is an energetic nitrating agent; it converts benzene and its homologs, and many classes of organic bodies to mono nitro derivatives in theoretical yield.³⁸ The compound has been employed for the nitration of esters which are readily hydrolyzed, such, for example, as methyl opianate.³⁹ This reagent directs the nitro group to the *ortho* position in substituted benzenes, such as toluene, benzyl chloride, and acetanilide, and yields mono nitro derivatives.⁴⁰ Nitrobenzene and quinone are not nitrated by this compound.

Acetyl nitrate may be prepared by adding nitric anhydride to an equal weight of acetic anhydride and fractionally distilling the mixture under reduced pressure. The compound distills over at 22° under 70 mm pressure. Extreme care must be exercised in preparing acetyl nitrate, as the compound is a powerful explosive.³⁸

Benzoyl nitrate, $\text{C}_6\text{H}_5\text{OONO}_2$, like acetyl nitrate, is a powerful nitrating agent, and is capable of nitrating many classes of aromatic compounds.⁴¹ It is best used in solution in carbon tetrachloride or chloroform.⁴² Like acetyl nitrate, it induces *ortho* nitration, and yields mono nitro compounds almost exclusively and in excellent yield. The compound reacts normally with toluene, xylene, and mesitylene to form nuclearly nitrated products, but reaction with durene results in the formation of 2,4,5-trimethylphenylnitromethane. Side-chain substitution takes place also with pentamethylbenzene and hexamethylbenzene.¹¹ β -Naphthol reacts with benzoyl nitrate with difficulty, but β -naphthol methyl ether reacts readily to form 1-nitro-2-naphthol methyl ether. Benzaldehyde cyanohydrin is converted to nitromandelonitrile, $\text{C}_6\text{H}_5\text{C}(\text{NO}_2)(\text{OH})\text{CN}$, vanillin to 3-nitrovanillin, and coumarin to 5-nitrocoumarin, when treated with the reagent.⁴³ Many other aldehydes, including benzaldehyde and salicylaldehyde, are simply oxidized by the action of benzoyl nitrate. A few secondary aromatic amines give the corresponding nitramines in excellent yield under the action of this reagent.⁴⁴

Benzoyl nitrate is prepared by adding finely powdered silver nitrate in 20% excess, in small portions, to benzoyl chloride cooled to -15° , allowing the mixture to stand at

this temperature for an hour, and then filtering through dry filter paper. The product thus obtained contains 15 to 20% benzoic anhydride from which benzoyl nitrate cannot be separated. The product should be carefully protected from atmospheric moisture during and after its preparation. A *violent explosion* may result if the reaction product is accidentally filtered through a moist filter paper.

Diacetylorthonitric acid, $(\text{CH}_3\text{CO})_2\text{N}(\text{OH})_3$, has been employed as a nitrating agent; its action is similar to that of a mixture of nitric acid and acetic anhydride. The products obtained with this reagent generally differ from those obtained with nitric acid.⁴⁵ In some instances the compound acts as an acetylating agent rather than a nitrating agent.

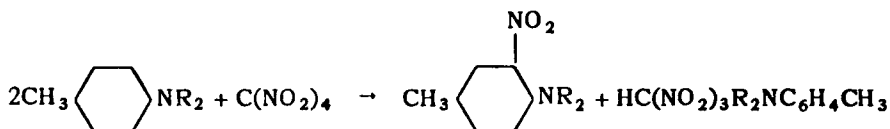
Diacetylorthonitric acid may be prepared by reacting acetic anhydride with nitric acid of density 1.4, or through the reaction of acetic acid with half a molecular equivalent of fuming nitric acid of density 1.52, and fractionally distilling the mixture. Practically the entire distillate, which boils between 127 and 128°, consists of diacetylorthonitric acid.⁴⁵

It is important to note that mixing of acetic acid with fuming nitric acid presents serious risks of explosion. The nitric acid employed should be free from nitrous acid, and care should be exercised to insure an entirely colorless mixture.⁴⁶

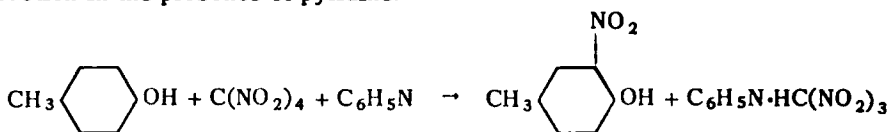
Nitration reactions may be carried out by means of *alkyl nitrates*. It is possible to effect the reaction in neutral or alkaline media when these reagents are used. The lower alkyl esters present the further advantage that the excess reagent may be readily eliminated from the reaction mixture after completion of the reaction, simply by boiling the mixture. Nitration with alkyl nitrates is almost invariably carried out in the presence of sodium- or potassium alcoholate. The reaction product is consequently the alkali metal derivative of the *aci* nitro compound, providing a mobile hydrogen exists in the molecule, allowing the rearrangement to the *aci* form to occur. Pyrrole, for example, gives the sodium

salt of pyrrole nitronic acid, $\overline{\text{CH} = \text{CH} \cdot \text{N} = \text{CH} \cdot \text{C}} = \text{NOONa}$, when treated with ethyl nitrate in the presence of sodium ethoxide. The nitro compound may be obtained from this salt by treatment with carbon dioxide.⁴⁷ The use of methyl nitrate is preferable to that of ethyl nitrate, since methyl nitrate is less stable and more readily hydrolyzed.⁴⁸

Tetranitromethane, $\text{C}(\text{NO}_2)_4$, has been employed as a nitrating agent. Certain aromatic amines, among them N-dimethyl- and N-diethyl-*p*-toluidine and N-dimethyl-*p*-anisidine, are nitrated to their *m*-nitro derivatives by this reagent:

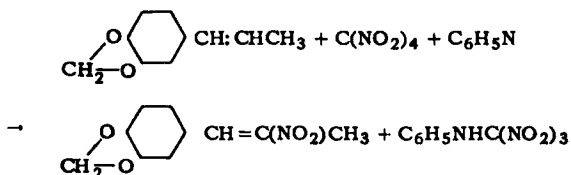


Non-basic compounds may be nitrated by this compound by carrying out the reaction in the presence of pyridine:

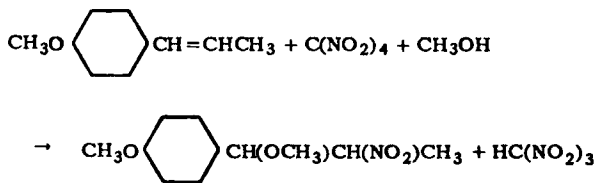


The use of this reagent makes possible the nitration of a compound in an acid-free medium.

The hydrogen in an olefinic double bond may be replaced with a nitro group under the action of tetranitromethane in the presence of pyridine; isosafrole, for example, gives β -nitroisosafrole:



Anethole, o-anethole, isoeugenol ether, aarone, isomyristicin, and isopiole are similarly nitrated in the side-chain, while safrole, o-estragole, eugenol ether, myristicin, and apiol are unaffected. If the reaction is carried out in alcoholic solution in the absence of pyridine, addition of a molecule of alcohol at the double bond also takes place:



The reaction in this case may be regarded merely as an addition of an alkyl nitrate at the double bond.

Hydroxy-Nitration; Wolffenstein-Bötters Reaction⁴⁹

Nitrophenols are produced on heating aromatic compounds with nitric acid or higher oxides of nitrogen in the presence of mercuric salts. The use of highly concentrated nitric acid or of mixed acids in conjunction with mercuric salts results only in nitration of the aromatic body. As the dilution of the acid is increased, hydroxynitration takes place to an increasing extent, until finally, the hydroxy nitro compound becomes the sole, or the principal product. Nitric acid of 50% strength is generally employed for satisfactory hydroxy nitration. Benzene gives nitrophenol, 2,4-dinitrophenol, and picric acid when subjected to this treatment, while toluene gives trinitrocresol and nitrohydroxybenzoic acid. Chlorobenzene gives chloronitrophenol, together with a considerable quantity of picric acid. Naphthalene is converted largely to nitronaphthol, though nitronaphthalene is also formed in appreciable quantity. Quinoline is converted to nitrohydroxyquinoline. Salts of manganese and aluminum have also been used in conjunction with the mercury compound.⁵⁰

Replacement of Other Groups by the Nitro Group

A bromine atom in *ortho* or *para* position in brominated phenols is replaceable with the nitrosyl group.⁵¹ The reaction of nitric acid with 1,3-diethoxy-4,6-dibromophenol results in the replacement of both bromine atoms with nitro groups;

in 1,3-dihydroxy-2,4,6-tribromobenzene, only the bromine atoms in 4 and 6 positions are thus replaced. *o*-Iodoanisole gives 1-iodo-4-nitroanisole by reaction with nitric acid; 1,6-dibromo-4-fluoroanisole is converted to 2,6-dibromoquinone.

In alkylated aromatic compounds, a halogen atom attached to the side-chain may be replaced with the nitro group by reaction with silver nitrate.⁵²

The *sulfo* group in many sulfonic acids is replaceable with a nitro group. *p*-Nitrophenol is thus readily obtained from phenol parasulfonic acid.⁵³ The sulfo group in guaiacolsulfonic acid may be replaced with the nitro group by heating with a large excess of dilute nitric acid.⁵⁴ α -Naphthol-2,4-disulfonic acid, which is readily obtained by dissolving α -naphthol in concentrated sulfuric acid, is converted to 2,4-dinitro- α -naphthol (Martius Yellow) by heating with dilute nitric acid.⁵⁵ Many sulfonic chlorides are also converted to nitro compounds by replacement of the chlorosulfonic group by treatment with nitric acid.⁵⁶

The *carboxyl* group in aromatic compounds may occasionally be replaced with a nitro group. In the nitration of *p*-dimethylaminobenzoic acid, for example, 2,4-dinitrodimethylaniline and 2,4-dinitromethylaniline are the products obtained.⁵⁷ The carboxyl group in dialkyl aminobenzoic acids is also replaced by treatment with nitrous acid.⁵⁸ Cinnamic acid, treated at 0° with nitric acid of density 1.52, reacts vigorously to give *ortho* and *para* ω -dinitrostyrenes. The reaction is suitable for the preparation of these compounds. Nitrocinnamic and nitrochlorocinnamic acids give the corresponding dinitrostyrenes by this treatment.⁵⁹

Alkyl groups attached to an aromatic nucleus have been replaced, in certain instances, with nitro groups during a nitration reaction. *p*-Cymene, for example, treated at -10° with nitric acid of density 1.42 and containing a little sulfuric acid, gives 2-nitro-*p*-cymene, together with about 8% of *p*-nitrotoluene formed by replacement of the isopropyl group with a nitro group.⁶⁰ Replacement of isobutyl groups attached to an aromatic nucleus with nitro groups has also been observed.⁶¹ The methylene nitrate group, $-\text{CH}_2\text{ONO}_2$, present in an aromatic body may be replaced with a nitro group. Some of the methyl groups in highly methylated benzenes are replaced with nitro groups on treatment with a mixture of fuming nitric acid and sulfuric acid; methylene nitrate formation probably precedes removal of the methyl group.⁶²

Nitro compounds may be prepared through the replacement of the *diazo* group in aromatic diazo compounds. The subject has been considered in Chapter 17 dealing with diazo compounds.

Preparation of Nitro Compounds from Amino Compounds

The amino group in primary aromatic amines may be converted to a nitroso group by oxidation with Caro's acid, i.e., potassium persulfate, in concentrated aqueous solution. The nitroso compound may be converted to the corresponding nitro compound by heating with nitric acid, or by oxidation with potassium ferricyanide or potassium permanganate.⁶³ Oxidation may also be effected with ferric chloride or sulfomonoperacid.⁶⁴

As an example, 5-nitrotoluidine is added to 43 parts of Caro's acid solution, and the mixture is allowed to stand for twelve hours. The nitrosonitrotoluene formed precipitates out as a solid and is filtered and washed with water. It is converted to the corresponding dinitro compound by heating on a water bath with fuming nitric acid until red fumes are no longer given off.

In a similar manner 2,3,4-, 2,4,5-, and 2,3,6-trinitrotoluenes have been made from the appropriate dinitrotoluidines.⁶⁵

The solution of Caro's acid is made by adding two parts of finely powdered ammonium persulfate to three parts of ice-cooled concentrated sulfuric acid with good stirring, and pouring the mixture onto twelve parts of crushed ice.

Nitration of Various Types of Compounds

Nitration of Benzene and its Homologs

Nitration of benzene with ordinary concentrated nitric acid does not proceed satisfactorily. Nitration may be accomplished with fuming nitric acid used in moderate excess. Dinitrobenzene may be obtained by treating the hydrocarbon with hot fuming nitric acid. Benzene is usually nitrated, however, by use of "mixed acids."

Nitrobenzene is obtained, for example, by adding a mixture of 1.1 part of nitric acid of density 1.456 and 1.4 parts of sulfuric acid of density 1.842, with good agitation, to 1 part of benzene. The liquid is cooled during the initial stages of the addition of the mixed acid, then allowed to warm to 30-40°. After the introduction of all the acid, the mixture is allowed to stand for one hour, then the oily layer is drawn off, washed with water, dried with calcium chloride, and distilled. The yield is generally 95 to 96% of theory.⁶⁶ In commercial practice the hydrocarbon is added to the mixed acids in order to secure the maximum yield of the nitrated product.⁶⁷ Nitration proceeds rapidly when sulfuric acid of 85 to 99% concentration is employed, but slowly with 100% acid.⁶⁸ On further treatment with mixed acids, nitrobenzene is converted to *m*-dinitrobenzene.

The nitration of benzene to *dinitrobenzene* proceeds very rapidly when the hydrocarbon is added dropwise to a mixture of equal parts of fuming nitric acid and concentrated sulfuric acid. Addition of the benzene is continued as long as the hydrocarbon dissolves completely in the reaction mixture, then the liquid is boiled for a few minutes. In technical operation, the theoretically required amount of commercial nitric acid is used, mixed with concentrated sulfuric acid. Benzene has been converted to 2,4-dinitrophenol in 72% yield by adding it dropwise with stirring to 10.6 molar nitric acid containing 0.37 molal proportion of mercuric nitrate heated to 50°. ³⁹⁰

Ethyl nitrate reacts vigorously with benzene in the presence of anhydrous aluminum chloride, forming nitrobenzene.⁶⁹

Homologs of benzene are nitrated more readily than benzene itself. It would appear that the methyl group increases the reactivity of each *ortho* position about 28-fold, that of the *para* position about 35-fold, and of each *meta* position only twofold. As a rule, nitration proceeds the more readily, the greater the number of alkyl groups attached to the nucleus.⁷⁰ *o*-Xylene is less readily nitrated than *p*- and *m*-xylene.⁷¹ The formation of di- and trinitro compounds takes place more readily with homologs of benzene than with benzene itself. In fact, the most convenient method of preparation of trinitrobenzene appears to be the nitration of toluene, followed by oxidation of the methyl group, and subsequent decarboxylation of the trinitrobenzoic acid formed.

Mono nitro compounds of benzene homologs are formed smoothly by adding a mixture of slightly more than one molecular equivalent of nitric acid with concentrated sulfuric acid to the hydrocarbon with good agitation. More highly nitrated products are obtained by increasing the amount of the nitrating mixture, and carrying out the reaction at a higher temperature. The nitrating agent employed may exert an effect on the position of attachment of the nitro group; thus, toluene is converted largely to paranitrotoluene when treated with nitric acid alone, but it is converted principally to o-nitrotoluene when nitrated with mixed acids.²¹ The temperature and the amount of the reagent employed exerts an influence on the proportion of the isomers formed.

On mononitration of toluene, the product obtained consists of 57% of *ortho*-, 40% of *para*-, and 3% of *meta*-nitrotoluene.⁷² The *ortho* nitro compound gives, on further nitration, 2,4- and 2,6-dinitro derivatives, while the *para* nitro compound gives only the 2,4-dinitro derivative. Nitration of toluene with acetyl nitrate leads to the formation of o-nitrotoluene in 90% yield.⁷³ Trinitration of the hydrocarbon results in the formation of the 2,4,6-trinitro derivative as the major product, the 2,4,5-, 2,3,4-, and 2,3,6-trinitro derivatives forming 2.9, 1.3, and 0.3% of the total nitrated product, respectively.⁷⁴ *p*-Xylene gives, on nitration with mixed acids, 2,6- and 2,3-dinitro-*p*-xylene; further nitration gives trinitro-*p*-xylene.⁷⁵ *o*-Xylene does not give a trinitro derivative even when treated with a mixture of concentrated nitric acid and fuming sulfuric acid. Dinitro mesitylene is formed when *mesitylene* is added dropwise to an excess of fuming nitric acid externally cooled with ice.⁷⁶ The mono nitro compound is obtained only when the reaction is carried out in glacial acetic acid solution. Cumene, or isopropylbenzene, gives 4-nitro cumene with "mixed acids" at 5 to 10°.⁷⁷ *ψ*-Cumene is comparatively difficult to nitrate; the mono nitro compound is best prepared by the action of mixed acids under carefully regulated conditions.⁷⁸ *Durene* yields a dinitro compound with nitric acid, and all attempts to prepare a mono nitro compound by direct nitration have failed.⁷² *Ortho* and *para* dinitrocymene give 2,3,6-trinitrocymene on nitration with a mixture of fuming nitric acid and sulfuric acid.⁷⁹ *p*-Cymene or 1,4-methylisopropylbenzene is converted to 2-nitro-*p*-cymene.⁸⁰

Trinitrobutyltoluene, one of the so-called artificial musks, is prepared by adding butyltoluene slowly to five parts of a mixture of nitric acid of density 1.5 with two parts of sulfuric acid containing 15% of sulfur trioxide, and heating the mixture on the water bath for 8 to 9 hours. The nitrated body is recovered by pouring the mixture into water, and is put through the process of nitration once more. The product is finally isolated by once more pouring the reaction mixture in water and filtering the precipitated trinitro compound.

Mesitylene, treated with a solution of fuming nitric acid in a mixture of acetic acid and acetic anhydride at 15-20°, gives nitromesitylene.⁸¹

The nitration of benzene and its homologs with *nitrogen tetroxide*, N_2O_4 , in solution in sulfuric acid, proceeds at a satisfactory rate at a low temperature.³⁴ Toluene gives with this reagent 65% of o-nitrotoluene and 35% of p-nitrotoluene.

Benzene and its homologs have also been nitrated by means of *nitrosulfonic acid*.

Alkyl benzenes, heated in a sealed tube with dilute nitric acid, are nitrated in the side-chain. For example, ethyl benzene heated at 105-106° in a sealed tube with nitric acid of density 1.075, gives α -nitroethylbenzene, $C_6H_5CH(NO_2)CH_3$, in 44% yield. Isopropylbenzene similarly treated gives phenylnitroisopropane, $C_6H_5C(NO_2)(CH_3)_2$.⁸² Butylbenzene gives phenylnitrobutane, $C_6H_5CH(NO_2)CH_2CH_2CH_3$; isobutylbenzene gives

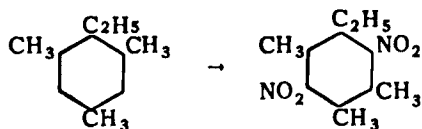
little phenylnitroisobutane, $\text{C}_6\text{H}_5\text{CH}(\text{NO}_2)\text{CH}(\text{CH}_3)_2$. Dibenzil gives with nitric acid of density 1.075 at 100° , diphenylnitroethylene, $\text{C}_6\text{H}_5\text{CH}(\text{NO}_2)\text{CH}_2\text{C}_6\text{H}_5$.⁸³ Toluene may be converted to phenylnitromethane, $\text{C}_6\text{H}_5\text{CH}_2\text{NO}_2$, in 50% yield by heating to 100° with nitric acid of density 1.12.⁸⁴ Secondary hydrogen atoms are replaced more readily than the primary, and the tertiary more readily than the secondary. Among secondary hydrogen atoms, those nearest a quaternary carbon atom are replaced preferentially.⁸⁵

Nitration of the side-chain may occur when polyalkyl benzenes are treated with benzoyl nitrate; one methyl group is nitrated in durol, for example, by this treatment.⁸⁶ Pentamethylbenzene gives a mixture in equal parts of the nuclearly and side-chain nitrated products.

Phenylnitromethane is converted to 3,5-dinitrophenylnitromethane with a 1:1 mixture of nitric acid and oleum at 65° .³⁹¹

Diphenyl has been converted to dinitrodiphenyl by covering the compound with two parts of concentrated nitric acid of density 1.45 and one-third part concentrated sulfuric acid, and allowing the mass to stand, finally boiling it for a short time.⁸⁷

Nitrating agents may bring about the *replacement of alkyl groups* with nitro groups in certain polyalkyl benzenes.⁸⁸ A tertiary alkyl group is most apt to be replaced;⁸⁹ replacement of a tertiary residue in trialkylbenzenes takes place readily. Isopropyl groups are also often replaced, though occasionally they are oxidized to an acetyl or carboxyl group.⁹⁰ Cymene, treated with nitric acid of density 1.52, gives 2,4-dinitrotoluene.⁹¹ Nitration of 1,4-diisopropylbenzene results in the formation of a mixture of 4-nitroisopropylbenzene and the normal nitration product, namely, 2-nitro-1,4-diisopropylbenzene.⁹² Alkyl benzenes containing more than three alkyl groups attached to the nucleus may behave abnormally when nitrated under drastic conditions. The alkyl group in meta position to the first entering nitro group is usually replaced with a nitro group in these compounds.⁶¹ Exceptions are pentamethyl and pentaethylbenzenes which yield dinitroprehnitene and *p*-dinitrotetraethylbenzene, respectively.⁹³ These same compounds also result on nitrating hexamethyl- and hexaethylbenzene, respectively. In ethylmesitylene, replacement of a methyl group as well as migration of a methyl group take place when the compound is treated with a mixture of fuming nitric acid and sulfuric acid.⁹⁴



It is believed that the replacement of methyl groups is preceded by the conversion of the methyl group into the methylene nitrate group, $-\text{CH}_2\text{ONO}_2$.

Nitration of polyalkylated benzenes may also result in the formation of nitric esters, with the nitro group attached to a methyl or other alkyl group.⁹⁵

Nitration of Naphthalene and Other Polynuclear Hydrocarbons

Naphthalene is very readily nitrated, at or somewhat above room temperature, by concentrated nitric acid, the nitro group entering both the α - and β -positions.⁹⁶ When the reaction is carried out at higher temperatures, 1,5- and 1,8-dinitronaphthalenes are obtained. It is preferable, however, to carry out the

nitration by use of mixed acids.⁹⁷ When dinitration with mixed acids is carried out at the lowest possible temperature, the 1,8-, or β -dinitro derivative is formed, while if the reaction is effected at a higher temperature, the 1,5- or α -dinitro isomer is obtained.⁹⁷ Further nitration of α -nitronaphthalene leads to the formation of 1,5- and 1,8-dinitronaphthalenes. Nitration of 4- and 5-nitro-1-methylnaphthalenes results in the formation of 4,5-dinitro-1-methylnaphthalene.⁹⁸ β -Methylnaphthalene is readily nitrated by dilute nitric acid.⁹⁹ Nitration of naphthalene takes place energetically, and polynitro compounds are formed readily.

Mononitronaphthalene has been prepared by adding 128 gm of naphthalene to a mixture of 105 gm of 62% nitric acid and 300 gm of 80% sulfuric acid, heating the mixture with stirring first at 50° for six hours, and then at 60° for one hour. The crystals that separate on cooling contain 90–92% of α -nitronaphthalene, 4–5% of the β -nitro compound, 2–3% dinitronaphthalene, and about 0.5% of 2,4-dinitro-1-naphthol.

Certain difficultly accessible nitronaphthalenes have been prepared from nitrotetralins.¹⁰⁰

Tetralin, treated with mixed acids of less than 25% water content at a temperature not exceeding 50°, gives α - and β -nitrotetrahydronaphthalene. When the hydrocarbon is treated with a mixture of 4 parts of nitric acid of density 1.47 and 5 parts of sulfuric acid monohydrate, it is converted to 1,3-dinitrotetrahydronaphthalene.¹⁰¹ The use of concentrated nitric acid of density 1.5 appears to be preferable, however, for the preparation of dinitrotetralene.¹⁰²

Anthracene is oxidized to anthraquinone when treated with nitric acid.¹⁰³ 9-Nitroanthracene has been prepared, however, by carrying out the nitration in acetic acid below 30° with nitric acid of 1.42 density, adding a mixture of concentrated hydrochloric acid and glacial acetic acid to the filtered liquid, and triturating the resulting 9-nitro-10-chloro-9,10-dihydroanthracene formed with 10% aqueous sodium hydroxide at 60 to 70°. ³⁹²

Phenanthrene in acetic acid solution, treated with a mixture of nitric acid of density 1.45 with acetic anhydride, first at room temperature for 1 to 2 hours, then at water bath temperature, is converted principally to 9-nitrophenanthrene.¹⁰⁴ Small amounts of 2-, 3-, and 4-nitrophenanthrenes are also formed. Phenanthrene in powdered form, treated with liquid nitrous acid in a freezing mixture for 20 hours is converted to mononitrodihydrophenanthrene.¹⁰⁵ *Dihydrophenanthrene* has been converted to its 2-nitro derivative by treatment with a solution of nitric acid of density 1.4 in 4 parts of glacial acetic acid.¹⁰⁶ *Fluorene*, treated at 50–60° with 1.3 molecular proportions of nitric acid of density 1.42 in solution in acetic acid, is converted to 2-nitrofluorene in 78–80% yield. *Acenaphthene*, subjected to the action of nitric acid mixed with acetic anhydride, gives nitroacenaphthene.¹⁰⁷

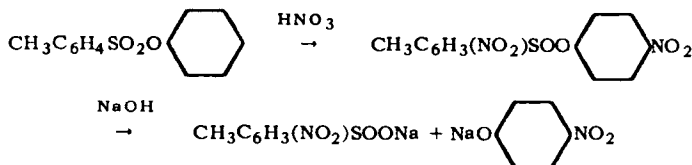
Nitration of Phenols and Naphthols

Phenols undergo nitration with great readiness, and are easily nitrated with nitric acid alone, or with nitric acid mixed with acetic acid. Phenol is nitrated even by boiling 3% nitric acid.¹⁰⁸ The presence of a little nitrous acid in the nitric acid employed seems to be necessary for successful nitration.¹⁰⁹ *Phenol* itself is nitrated satisfactorily by the action of six times its weight of 30% nitric acid at 5–10°, completion of the reaction requiring about two hours. The product obtained consists of a mixture of *o*- and *p*-nitrophenols in about equal

amounts together with some indophenol N-oxide, $\text{HOC}_6\text{H}_4\text{NO} = \text{C}_6\text{H}_4 = \text{O}$.¹¹⁰ The isomers may be separated by steam distillation, which removes the more volatile *o*-nitrophenol, leaving behind the *para* compound. Better yields are obtained when the nitration is carried out by use of concentrated nitric acid alone or in admixture with acetic acid. When acetic acid is used in the reaction, the formation of the *ortho* nitro compound is favored, and the *ortho* compound is formed exclusively when phenol is nitrated at 45° with a mixture of acetic acid and cupric nitrate. Tarry matter is formed in varying quantity in the reaction of nitric acid with phenols. This difficulty is avoided effectively by carrying out the reaction in glacial acetic acid at a low temperature, usually between -15 and -10° .¹¹¹ Chloroform has also been used as a diluent to moderate the action of nitric acid, as for example, in the preparation of nitrodurol.¹¹² Benzene has also been used for this purpose. *p*-Cresol, for instance, has been nitrated to *o*-nitro-*p*-cresol in benzene solution.¹¹³ By introducing a substituent at one of the positions 2 or 4, the nitro group is forced to enter the position remaining free.

o-Nitrophenol is prepared in the following manner: Phenol is first converted to phenol-*p*-sulfonic acid with sulfuric acid at 100 – 120° , and the sulfonic acid is treated with nitric acid or with "mixed acids."¹¹⁵ The nitrated phenolsulfonic acid, isolated as the sodium salt, is added to the calculated quantity of sulfuric acid; the mixture is heated in an oil bath to 150° and a current of steam, also heated to 150° , is passed through the liquid, whereupon orthonitrophenol distills over.

p-Nitrophenol is obtained by nitrating the *p*-toluenesulfonic ester of phenol, and treating the nitrated compound formed with aqueous caustic;¹¹⁶



The second reaction takes place rapidly on heating the nitrated ester with aqueous sodium hydroxide at 100° . The sodium *p*-nitrophenolate crystallizes out on cooling the solution. Phenyl *p*-toluenesulfonate is formed by adding *p*-toluenesulfonyl chloride to a hot solution of an equivalent amount of sodium phenolate, and crystallizes out on cooling the solution.

The use of nitric acid in admixture with acetic acid is illustrated by the preparation of nitro-*o*-cresols: The cresol is dissolved in an equal weight of acetic acid, and the solution is added slowly and with good stirring, to a mixture of strong nitric acid with two or three parts of glacial acetic acid. The nitric acid should be in excess over the theoretical, about 1.7 to 2.5 moles per mole of cresol. The greatest care must be exercised to maintain the temperature at about -10° during the reaction. After completion of the nitration, the mixture is poured into ice and the solid nitrocresols which separate are filtered off and subjected to steam distillation. The *ortho* compound, which forms the larger proportion of the nitrated products, distills over, leaving behind the 5-nitro compound.

m-Cresol has been nitrated similarly by adding its solution in an equal weight of acetic acid cooled to -5° to two parts by weight of a mixture consisting of 1 part by weight of nitric acid of density 1.5 with 2 parts of acetic acid, cooled to -15° . Nitration is complete in the course of $1\frac{1}{2}$ hours, during which time the temperature of the liquid should

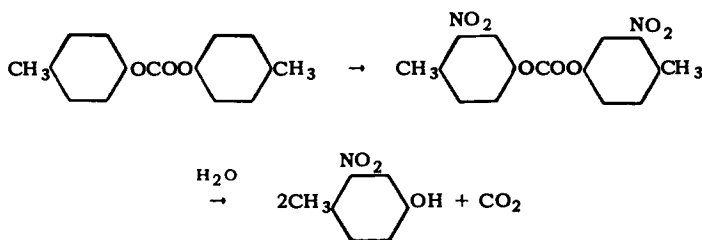
not be allowed to exceed -1° . The nitrated product is recovered by pouring the reaction mixture into about $2\frac{1}{2}$ times its weight of a mixture in equal parts of ice and water, and allowing the mass to stand overnight. The isomers are separated by steam distillation, the more volatile 4-nitro-*m*-cresol distilling over, and the 6-nitro isomer remaining in the still residue. The two isomers are obtained in the ratio 1 to 1.3. The total yield of mononitro cresols is a little more than 50% of the theoretical.¹¹⁷

Nitration of *m*-cresol with a mixture of nitric and fuming sulfuric acids of 6 to 7% sulfur trioxide content results in the formation of 4-nitro-*m*-cresol.¹¹⁸

2-Nitro-*m*-cresol has been obtained by nitrating resorcinolsulfonic acid with a mixture of 90% nitric acid with three parts by weight of strong sulfuric acid, and hydrolyzing the nitrated sulfonic acid formed by distillation with superheated steam.¹¹⁸

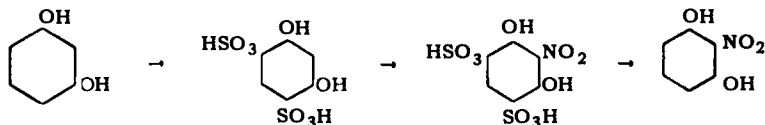
When *p*-cresol is nitrated at a low temperature with a mixture of nitric and acetic acids, only 3-nitro-*p*-cresol is obtained, a compound which is volatile with steam.

2-Nitro-*p*-cresol is prepared by nitrating *p*-tolylcarbonate with a mixture of nitric and sulfuric acids at $4-9^{\circ}$, and hydrolyzing the nitrotolyl carbonate formed:¹¹⁹



The 3-nitro isomer is formed in 2-3% yield, but can be eliminated by steam distillation. *p*-Tolyl carbonate is prepared through the reaction of two molecular equivalents of sodium *p*-cresylate in aqueous solution with one of phosgene.

2-Nitroresorcinol has been prepared through the disulfonation of resorcinol with seven parts by weight of 20% oleum at $90-100^{\circ}$, and nitration of the product at $10-15^{\circ}$ by the addition of 0.6 part 90% nitric acid mixed with three times its weight of strong sulfuric acid. Upon completion of the reaction, the mixture is added to six parts of water and subjected to distillation with superheated steam, whereupon 2-nitroresorcinol distills over as a light red crystalline body:¹²⁰



Nitropyrocatechol has been obtained by treating a 2% ethereal solution of pyrocatechol with fuming nitric acid, the reaction requiring about 24 hours for completion.¹²¹ *Eugenol* has been similarly nitrated to *nitro-eugenol*.

More than one nitro group is introduced in phenols by using a sufficiently large amount of nitric acid, and carrying out the reaction at a higher temperature; at $0-5^{\circ}$, for example, if it is desired to introduce two nitro groups. The preparation of dinitrophenols is rendered difficult by the fact that phenolic bodies are readily converted to trinitro derivatives. Dinitro compounds may often be made, however, without difficulty by nitrating sulfonated phenols, and subsequently removing the sulfonic group. Dinitrophenol has been prepared, for example, by first sulfonating phenol at $130-140^{\circ}$ with twice its weight of strong sulfuric acid

and subjecting the cooled and diluted solution of the sulfonic acid at 45–50° to the action of seven parts of 30% nitric acid for a long period.¹²² Some picric acid also forms in this reaction which, however, can be removed by extraction with boiling water.

2,4-Dinitrophenol has been obtained in good yield by nitrating *p*-nitrosophenol,¹²³ a compound which is readily prepared by treating phenol with sodium nitrite and sulfuric acid.¹²⁴ In practice, dinitrophenol is almost exclusively prepared by heating 2,4-dinitrochlorobenzene with aqueous caustic, and decomposing the sodium dinitrophenolate formed with acid.

For the nitration of phenol to *trinitrophenol*, or picric acid, the action of nitric acid is moderated by converting phenol to its di- or trisulfonic derivative and subjecting this to the action of nitric acid. Even when this procedure is followed, it is necessary to cool the mixture during the early stages of nitration, although the reaction must be completed by heating on a water bath. Picric acid crystallizes in the pure form when the final reaction mixture is cooled.¹²⁵ An alternative procedure is to convert phenol first to dinitrophenol sulfonic acid, and to replace the sulfonic group in this with a nitro group by reaction with sodium nitrate in aqueous solution. Conversion of phenol to the dinitrosulfonic derivative is effected by heating at 80° with an equal weight of sulfuric acid, adding two equivalents of sodium nitrate to the cooled mixture, and heating gradually to 100°, then finally at 140° until the complete disappearance of the solid nitrate. The dinitrosulfonic compound is isolated by diluting the reaction mixture with water, adding an excess of lime, filtering the precipitated calcium sulfate together with the excess lime, and evaporating the filtrate to a small volume; upon acidification, the dinitrosulfonic compound precipitates out. Replacement of the sulfonic group by a nitro group is brought about by treatment at 140° for two hours with an aqueous solution of sodium nitrate.¹²⁶ The vigor of the reaction of nitric acid with phenol in the preparation of trinitrophenol has also been moderated by using a mixture of nitric acid of density 1.4 with one-third part of ethyl alcohol.¹²⁷

Phenol has been nitrated by use of nitrogen peroxide, N_2O_4 . Treatment of phenol in solution in benzene or petroleum ether with an equal weight of nitrogen peroxide in a cooling mixture results in the formation of *o*- and *p*-nitrophenols.¹²⁸ With liquid nitrogen peroxide at 0°, 2,4-dinitrophenol is obtained. *o*-Cresol gives *o*- and *p*-nitrocresols in almost equal quantities.¹²⁹

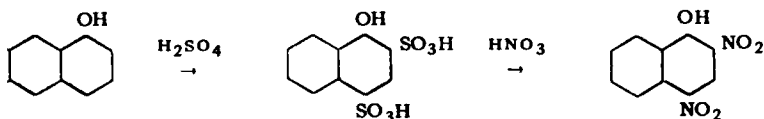
Nitrogen peroxide often causes the replacement of *sulfonic groups* in phenols with nitro groups. The reaction proceeds readily when nitrogen peroxide is passed through an aqueous solution of the phenol sulfonic acid. 3,5-Dinitrocresol has been obtained in this manner from *o*-cresol-3,5-disulfonic acid, and 3,5-dinitro-*p*-cresol from *p*-cresol-3-sulfonic acid. Methoxyl groups may be demethylated and carboxyl groups may be removed by this treatment.

Alkyl nitrites may act as nitrating agents toward phenols when they are made to react with the latter in the presence of oxygen. The reaction of phenol with amyl nitrite in the absence of a solvent takes place vigorously with the formation of only a small amount of *o*-nitrophenol. The reaction proceeds more slowly in ethereal solution with the formation of *p*-nitrophenol. *o*-Cresol in ethereal solution gives 3,5-dinitro-2-hydroxy-1-methylbenzene, and *m*-cresol gives 6-nitro-3-hydroxy-1-methylbenzene. Many other phenolic compounds, including guaiacol, resorcinol, phlorglucinol, pyrogallol, and thymol, have been nitrated by this method.¹³⁰

Certain chlorinated phenols have been converted to nitrophenols by adding solid sodium nitrite to their solution in acetic acid.¹³¹

Naphthols are readily acted upon by nitric acid,¹³² but these compounds are best nitrated by first converting them to their sulfonic derivatives, and heating these with nitric acid.¹³³

Martius Yellow, or 2,4-dinitro-1-naphthol, has been prepared, for example, by dissolving α -naphthol in an equal weight of concentrated sulfuric acid, and treating the solution with absolute nitric acid:¹³³



The compound is formed also by treating Schäffer's acid, i.e., α -naphthol-2-sulfonic acid, with nitric acid.¹³⁴ It is formed, further, by nitrating α -naphthylamine¹³⁵ or the diazonium compound derived from this base.¹³⁶

Energetic sulfonation of α -naphthol results in the formation of 1-naphthol-2,4,7-trisulfonic acid, and this, on treatment with nitric acid, is converted to *Naphthol Yellow*, or 1-naphthol-2,4-dinitro-7-sulfonic acid.¹³⁷

Mononitronaphthols are obtained in the form of their sodium salts by nitrating acetylnaphthylamines and boiling the nitrated naphthalides with caustic solution:¹³⁸



From α -acetylnaphthalide, the 2- and 4-nitro-1-naphthols are obtained, while the β -compound yields only the 1-nitro derivative.¹³⁹ Mononitronaphthols are also obtained from naphthols by treatment with nitrous acid and oxidation of the resulting nitrosonaphthols with potassium ferricyanide or dilute nitric acid.¹⁴⁰ α -Naphthol, treated in a cooled ethereal solution with *nitrogen peroxide*, gives 2-nitro-1-naphthol and 2,4-dinitro-1-naphthol; 2-naphthol gives 1,6- or 1,7-dinitro-2-naphthol.¹⁴¹ α -Nitronaphthalene, heated with finely pulverized caustic, is converted to 1-nitro-naphthol-2.¹⁴²

Trinitronaphthol has been prepared from dinitronaphthol in suspension in a large excess of concentrated sulfuric acid by the action of nitric acid,¹⁴³ although reaction is slow and complete only in about 10 days.¹⁴³

The reaction of nitric acid with dinaphthomethane results in the formation of nitrosonaphthol by cleavage of the molecule.¹⁴⁴ "Diquinatrole" or methylene-bis- α -nitro-2-naphthalene has been obtained, however, by carrying out the nitration under milder conditions with nitrous acid, namely, at room temperature in ethereal solution, generating the nitrous acid through the reaction of sodium nitrite with dilute acetic acid:¹⁴⁵



The reaction is complete within about two days.

Nitration of Phenol Ethers and Esters

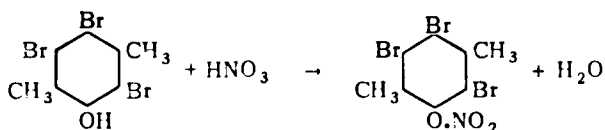
Ethers of phenols are nitrated readily, and their behavior on nitration is comparable to that of the corresponding phenols.¹⁴⁶ Anisole and phenetole are converted to 2,3,4,6- and 2,3,5,6-tetranitro derivatives.¹⁴⁷ Anisole gives *o*-nitroanisole when treated with benzoyl nitrate, while veratrole is converted quantitatively to 3-nitroveratrole by this reagent.

Nitration of α -alkoxynaphthalenes occurs successively at 2, 4, and 5 positions;¹⁴⁸ nitration of β -alkoxynaphthalenes yields the 1,6,8-trinitro derivative.¹⁴⁹ Benzoyl nitrate brings about the nitration of methyl and ethyl ethers of α - and β -naphthol, the former giving the 4-nitro derivatives, the latter the 2-nitro compounds.

Esters of phenols are nitrated with greater difficulty than phenols. The phenyl ester of 2,4,6-trinitrobenzoic acid, for example, must be heated to 70° for 15 minutes with 90% nitric acid in order to convert it to the *p*-nitrophenyl ester, while the preparation of *o,p*-dinitrophenyl ester requires the use of mixed acids and heating for five minutes at 125°.¹⁵⁰

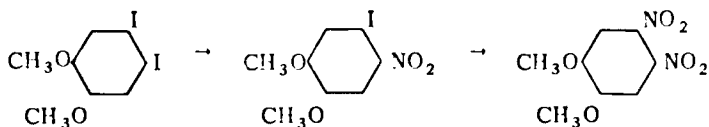
Abnormal Behavior of Phenols and Phenol Ethers

Fully brominated higher phenols react with nitric acid to form nitric esters; an ester is obtained, for example, from tribromo-*p*-xylenol:¹⁵¹



A bromine atom in certain brominated compounds is exchanged for a nitro group when the compounds are subjected to the action of nitric acid. Such an exchange is observed with 3,5-dibromo-4-hydroxyacetanilide, 2,6-dibromothymol and tribromoresorcinol; the last named give on nitration 2-nitro-6-bromo- and 2,4-dibromo-6-nitro derivatives respectively. An exchange of a carboxyl group in halophenol carboxylic acids for the nitro group is also observed. 3,5-Dibromosalicylic acid, for example, gives on nitration 2,4-dibromo-6-nitrophenol.¹⁵²

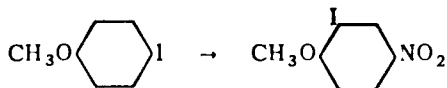
Exchange reactions of this type are also observed with phenolic ethers. The isopropyl and *tert*-amyl groups are replaced by nitro groups when isopropyl- and *tert*-amyl-*m*-cresol methyl ethers are treated with a glacial acetic acid solution of nitric acid.¹⁵³ The acetyl group in 3,4-dimethoxyacetophenone is replaced with nitro groups on nitration and 4,5-dinitroveratrole is formed.¹⁵⁴ The iodine atoms in 4,5-diiodoveratrole are replaced with nitro groups on nitration:



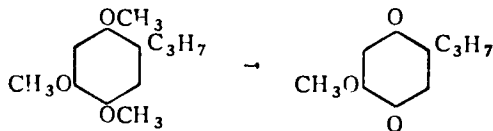
The nitration of 4-bromo-4'-nitrodiphenyl ether results in the formation of 2,4,-

2',4'-tetranitrodiphenyl ether, with replacement of the bromine atom with a nitro group. The nitration of 4-methyl-2'-nitro-4'-chlorodiphenyl ether causes the cleavage of the ether linkage, with the formation of 2,6-dinitro-4-chlorophenol. The formyl group in methylenedioxybenzaldehydes is also replaceable with a nitro group.¹⁵⁵

Nitration of 4-iodoanisole results in the formation of 2-iodo-4-nitroanisole:¹⁵⁶



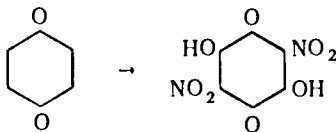
Nitric acid may cause the demethylation and oxidation of certain polyphenolic methyl ethers.¹⁵⁷ 1-*n*-Propyl-2,4,5-trimethoxybenzene, for example, treated with fuming nitric acid at -18°C , is converted largely to 2-*n*-propyl-5-methoxyquinone:



A small amount of 2-*n*-propyl-5-nitroquinone methyl ether is also formed. The latter becomes the principal product if the nitration is carried out at 50° with a 45% solution of nitric acid in glacial acetic acid. The isomeric 1-*n*-propyl-2,3,5-trimethoxybenzene is partially demethylated and oxidized when subjected to the action of 25% nitric acid at 25° . 2,5-Dimethoxy-3,4,6-trimethylbenzaldehyde gives on nitration 2,3,5-trimethyl-6-nitroquinone.

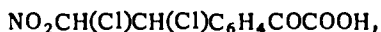
Nitration of Quinones

Nitrodihydroxyquinone results when nitrodiiminoquinone is heated; the latter compound is obtained by nitrating diamino- or diiminoquinone.¹⁵⁸ Nitrodihydroxyquinone is formed also when diaminoresorcinol is nitrated and the product is treated with aqueous potassium hydroxide solution.¹⁵⁸ *Benzoquinone*, subjected to the prolonged action of nitric acid of density 1.459 at -5 to -10° , is converted to *p*-dinitro-*p*-hydroxyquinone or *nitranilic acid*:¹⁵⁹



The compound is obtained also when dinitrohydroquinone is introduced carefully into an ice-cooled mixture of 3 parts of concentrated nitric acid and 6 parts of acetic acid.¹⁶⁰ The compound is formed further by heating chloranil in acetic acid solution with sodium nitrite,¹⁶¹ and from *p*-dihydroxyquinone by treatment with nitric acid.¹⁶² Nitranilic acid results also on nitrating diacetylanthraquinone, and this appears to be the most satisfactory method of preparation of the compound.¹⁶³

1,2-Naphthoquinone gives on nitration 3-nitro-1,2-naphthoquinone. The latter forms an addition product with chlorine which readily undergoes ring fission to give *o*-(α,β -dichloro- β -nitroethyl)benzoylformic acid,



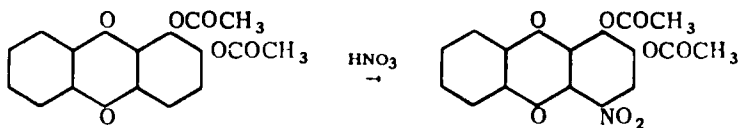
and this, on oxidation with chromic acid, yields ω,ω -nitrochloromethylphthalide,



Direct nitration of anthraquinone with mixed acids leads to the formation of dinitro derivatives.¹⁶⁵ The 1,5- and 1,8-dinitro compounds form the major portion of the nitrated product, with lesser amounts of the 1,6-, 1,7-, and 2,7- dinitro products. Nitric as well as sulfuric acid also exerts a definite oxidative effect.¹⁶⁶

1-Nitroanthraquinone has been prepared by heating anthraquinone at 100° for one hour with six parts of concentrated sulfuric acid and 2 parts of nitric acid of specific gravity 1.22.¹⁶⁷ Another procedure employed is to heat 3 parts of anthraquinone with 18 parts of sulfuric acid of 66° Bé and 1 part of nitric acid of 40° Bé at 50°.¹⁶⁸ The compound may be purified by vacuum distillation. The 2-nitro derivative is obtained by diazotizing 2-aminoanthraquinone and treating the diazonium salt with copper and sodium nitrite.¹⁶⁹

Alizarin, or 1,2-dihydroxyanthraquinone, in solution in fuming sulfuric acid, nitrated at -5 to -10° with a mixture of potassium nitrate and sulfuric acid monohydrate, is converted to α -nitroalizarin.¹⁷⁰ Nitration with sulfuric acid of density 1.84 and nitric acid gives principally the β -nitro compound. Dibenzoyl-alizarin, nitrated with mixed acids and subsequently debenzoylated, gives α -nitroalizarin.¹⁷¹ Nitration of diacetylalizarin proceeds readily, and results in the formation of diacetyl-4-nitroalizarin:



The boric ester of alizarin gives on nitration the β -nitro derivative. The ester is obtained readily by adding boric acid to a solution of alizarin in concentrated sulfuric acid. Hydroxyanthraquinone, flavopurpurin, anthrapurpurin, and other alizarin analogs may be converted to β -nitro derivatives by this method. The nitrated boric esters may be readily hydrolyzed to the nitrated hydroxyanthraquinones by boiling with water or dilute acids.

Anthraquinone-1-sulfonic acid, treated with "mixed acids" at 80–90° for six to eight hours, gives 1,5- and 1,8-nitrosulfonic acids. Nitration of alizarin α - and β -sulfonic acids takes place more readily when nitrous, rather than nitric acid is employed as the nitrating agent.¹⁷²

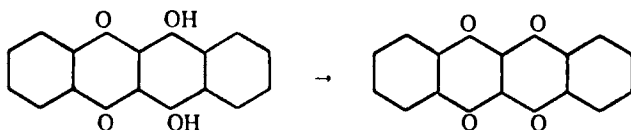
Nitrated haloanthraquinones are best prepared by nitrating haloanthraquinones.¹⁷³ The reverse procedure of chlorination of nitrated anthraquinones often results in the replacement of nitro groups with chlorine. Halonitro compounds

have been obtained on heating 1,5- and 1,8-nitroanthraquinonesulfonyl chlorides, by loss of sulfur dioxide.¹⁷⁴

The benzoyl derivatives of anthrapurpurin, or 1,2,7-trihydroxyanthraquinone, and flavopurpurin, or 1,2,6-trihydroxyanthraquinone, nitrated with "mixed acids" and debenzoylated, are converted to their α -nitro derivatives.¹⁷⁵ Such nitro compounds are not otherwise accessible.

Fluorenone, treated with cold concentrated nitric acid, is converted to an unstable nitrate. When the quinone is boiled with red fuming nitric acid for three hours, it is converted to 2,7-dinitrofluorenone.¹⁷⁶ Treated with a boiling mixture of fuming nitric acid and sulfuric acid, fluorenone is converted to 2,6,7-trinitrofluorenone.¹⁷⁶

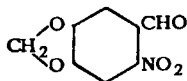
Dihydroxynaphthacenequinone is converted to naphthacenediquinone when subjected to the action of concentrated nitric acid:¹⁷⁷



Nitration of Aromatic Aldehydes

Aromatic aldehydes may be satisfactorily nitrated with nitric acid at a sufficiently low temperature.¹⁷⁸ Nitrobenzaldehyde may be obtained in good yield by treatment with nitric acid at a low temperature. Pure nitric acid combines in the cold with aromatic aldehydes forming molecular compounds, the so-called aldehyde nitrates, which readily change to nitrobenzaldehydes.¹⁷⁹ Benzaldehyde nitrate, $C_6H_5CHO \cdot HNO_3$, is formed on treating benzaldehyde with nitric acid of density 1.371. The nitrate is converted to the diacetate of *p*-nitrobenzaldehyde when added to acetic anhydride. Conversion to nitrated aldehyde has also been brought about by adding the aldehyde nitrate to sulfuric acid.

On adding *m*-methoxybenzaldehyde to nitric acid of density 1.46 at 0° and allowing the mixture to stand at 10° for one hour, two isomeric nitro aldehydes are formed.¹⁸⁰ Treatment of *piperonal* with nitric acid of density 1.48 at 6° results in the formation of pure *o*-nitropiperonal,¹⁸¹



Vanillin is completely oxidized when treated with concentrated nitric acid; the compound may be satisfactorily nitrated, however, when its hydroxyl group is protected by esterification or etherification.¹⁸² The isopropyl group in *thymol* is replaced with a nitro group when the compound is nitrated.¹⁸³

m-Nitro-*p*-hydroxybenzaldehyde is readily obtained by adding a little more than the calculated amount of nitric acid of density 1.4 to a solution of 1 part *p*-hydroxybenzaldehyde in 4 parts of glacial acetic acid, and gently warming the mixture.¹⁸⁴

Isovanillin has been converted to *o*-nitroisovanillin by adding to a 25% acetic solution of the compound, gradually and with stirring, a volume of concentrated nitric acid equal to 1/10 that of the solution, at 10° and allowing the mixture to stand half an hour. On pouring the liquid into cold water, the nitrated compound gradually separates as a crystalline mass.¹⁸⁵

Salicylaldehyde, treated with fuming nitric acid with ice-cooling, gives two isomeric nitrosalicylaldehydes, the 5- and 3-nitro derivatives.¹⁸⁶

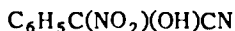
The oxidative effect of nitric acid toward aldehydes is largely eliminated when a mixture of nitric and sulfuric acids is used as the nitrating agent.

The procedure adopted in nitrating *benzaldehyde* is as follows:¹⁸⁷ The aldehyde is run into the mixed acid containing 28 to 30% nitric acid, with good agitation at 0 to 5°. After stirring for a short time, the liquid is poured on ice. The product consists of *m*-nitrobenzaldehyde and the isomeric *ortho* compound which forms about 20% of the total. The *meta* isomer is separated by allowing the product to solidify partially and filtering the solid *meta* product, which is obtained in 65% yield. The *ortho* isomer present in the oil cannot be separated in the pure form.

o-Nitro-*m*-chlorobenzaldehyde has been prepared by adding *m*-chlorobenzaldehyde very slowly and with good stirring, to a mixture of nitric acid with about twenty times its weight of sulfuric acid cooled to 0°. A few hours after the completion of the reaction the mixture is poured on ice and the nitroaldehyde isolated by filtration.¹⁸⁸

m-Nitroanisaldehyde, or 3-nitro-4-methoxybenzaldehyde, is obtained when *anisaldehyde* is treated with a mixture of 1 part of nitric acid with 20 parts of concentrated sulfuric acid, below 0°. After the completion of the reaction, the mixture is allowed to stand one hour, and is then diluted with a large volume of water, whereupon the nitro compound separates as an oil.¹⁸⁹ When the nitration is carried out a few degrees above zero, two nitro groups enter the nucleus, both *meta* to the aldehyde group.¹⁹⁰

Benzoyl nitrate causes the oxidation of benzaldehyde, anisaldehyde, salicylaldehyde and its methyl ether, without bringing about their nitration. Benzaldehyde cyanohydrin is converted by this reagent to nitromandelonitrile,



vanillin is converted quantitatively to 3-nitrovanillin, and coumarin to 5-nitrocoumarin.⁴³ β -Naphtholaldehyde, treated with a carbon tetrachloride solution of benzoyl nitrate, gives a dinitro derivative in quantitative yield.

Various other methods have also been employed for the preparation of nitrated aromatic aldehydes. 2,4-Dinitrobenzaldehyde has been obtained by the oxidation of 2,4-dinitrobenzylaniline or its sulfonic acid,



with potassium permanganate or chromic acid. Schiff's bases are first formed in this reaction, and are subsequently decomposed by acid. This nitroaldehyde has also been obtained from the anil, $(\text{NO}_2)_2\text{C}_6\text{H}_4\text{CH} = \text{NC}_6\text{H}_4\text{N}(\text{CH}_3)_2$, which is prepared by the action of *p*-nitrosodimethylaniline on 2,4-dinitrotoluene.¹⁹¹ 2,6-Dinitrobenzaldehyde has been prepared from 2,6-dinitrotoluene by converting it first to the corresponding benzyl chloride, then successively to the anilide and anilidene and finally to the aldehyde by hydrolysis.¹⁹² 2,4,6-Trinitrobenzaldehyde has been prepared in a similar manner from 2,4,6-trinitrotoluene.¹⁹³

Nitration of Aromatic Acids

Some aromatic acids have been nitrated successfully with concentrated nitric acid. Phenylacetic acid, for example, treated with nitric acid in solution in acetic anhydride at ordinary temperature, gives principally *p*-nitrophenylacetic

acid.¹⁹⁴ Cinnamic acid, treated with ordinary nitric acid, gives its *ortho* nitro derivative,¹⁹⁵ though treatment with 100% nitric acid at 0° results in the formation of a mixture of β -2- and β -4-dinitrostyrenes. *Para*-substituted cinnamic acids in which the substituent is a halogen, nitro, amino, or methoxy group, behave similarly.

Aromatic acids are nitrated with moderate ease with mixed nitric and sulfuric acids. The nitro group enters the *meta* position, unless there are other groups in the nucleus tending to direct it elsewhere.

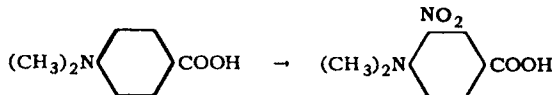
Benzoic acid may be nitrated by stirring it at 15° with concentrated sulfuric acid and adding concentrated nitric acid or potassium nitrate. Nitration is complete within a few hours, and the product may be separated by pouring the reaction mixture on ice.¹⁹⁶ *o*-Chlorobenzoic acid is readily converted by "mixed acids" to *o*-chloro-*m*-nitrobenzoic acid.¹⁹⁷ Treatment with a mixture of nitric acid and fuming sulfuric acid results in the formation of 2,4,6-trinitro-1-chlorobenzene.¹⁹⁸ 2,4-Dichlorobenzoic acid in solution in concentrated sulfuric acid, treated at 65–72° with "mixed acids" gives 2,6-dichloro-3-nitrobenzoic acid in 94% yield.¹⁹⁹ *o*-Fluorobenzoic acid gives the 2-fluoro-5-nitro acid as the principal product with nitric acid of density 1.52, at 80°; the *para* acid gives the 3-nitro-4-fluoro acid.³⁹³

Phthalic acid has been nitrated to 3- and 4-nitrophthalic acid with mixed acids.²⁰⁰ Pure 4-nitrophthalic acid may be obtained in 60 to 70% yield by treating phthalimide with mixed acids and hydrolyzing the resulting nitrophthalimide. *Terephthalic acid* is hardly acted upon by ordinary mixed acids at 50°, but can be successfully nitrated with a mixture of nitric and fuming sulfuric acids.²³

Nitrous acid is suitable for the nitration of *salicylic acid*.²⁰¹ *o*-*m*-Nitrosalicylic acid, or 2-hydroxy-5-nitrobenzoic acid may be obtained by mixing a solution of 100 gm of salicylic acid with 130 gm of sodium nitrite and 150 gm water, and adding 1.2 liters of sulfuric acid of density 1.52 cooled to at least 15°. After stirring the mixture for four hours, it is warmed to 50° and is then allowed to stand for a few hours, or until no more nitrous vapors are evolved. The compound is purified by repeated crystallization from water. *v*-*m*-Nitrosalicylic acid, or 2-hydroxy-3-nitrobenzoic acid may be made by mixing 100 gm of salicylic acid with 170 gm sodium nitrite and 150 gm water and adding 1 liter of sulfuric acid of density 1.52 warmed to 60°. Reaction proceeds very vigorously, and it is advisable to place the reaction vessel in a water bath before the addition of the acid. If the liquid fails to assume a red color, a further 100 cc of sulfuric acid should be added. On cooling the reaction mixture to room temperature, the acid separates as a precipitate. The compound is purified by repeated crystallization.

p-Aminosalicylic acid is readily and quantitatively nitrated to a mononitro derivative.

p-Dimethylaminobenzoic acid, nitrated with a mixture of sulfuric acid and 60% nitric acid at 5 to 10°, gives the normal nitration product:



When the reaction is carried out at 60–70°, a complicated mixture of replacement products and the normal nitrated compound results, containing some *p*-nitro- and 2,4-dinitro-dimethylaniline. Prolonged action of large amounts of nitric acid results in the formation of a number of other nitration products as well.

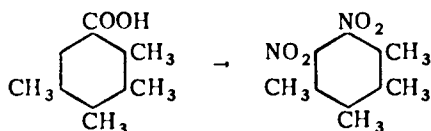
Esters of aromatic acids, such as ethyl benzoate, combine with nitric acid to form well characterized addition products;²⁰² these may be converted to nitro

compounds. Nitration of esters may, as a rule, be carried out in the same manner as that of acids. Occasionally the point of attachment of the nitro group may be different as the ester or acid are nitrated; cinnamic ester, for example, gives on nitration the *ortho* nitro product in 70% yield,²⁰³ while nitration of the acid leads to the formation of the *para* isomer. Occasionally use of the ester makes possible a process of nitration inapplicable to the acid; the methyl ester of 3-nitro-4-methylaminobenzoic acid, for example, may be converted to 3,5-dinitro-4-nitrosomethylaminobenzoic methyl ester on treatment with nitric acid of density 1.52 at 45°.²⁰⁴

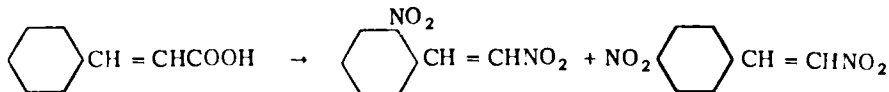
The nitration of *dimethyl terephthalate* to dimethyl nitroterephthalate has been effected in the following manner:²⁰⁵ One part by weight of terephthalic ester was added to a mixture of four parts of nitric acid of density 1.48 and six parts of sulfuric acid of 7% anhydride content in the course of ten minutes. The mixture was allowed to stand 30 minutes, with occasional cooling to avoid too vigorous a reaction, and was then poured into 15 parts of ice. The precipitated nitro compound was filtered, washed with dilute ammonia, and purified by crystallization from alcohol. The yield was 80 to 90% of theory.

Anomalous Behavior²⁰⁶

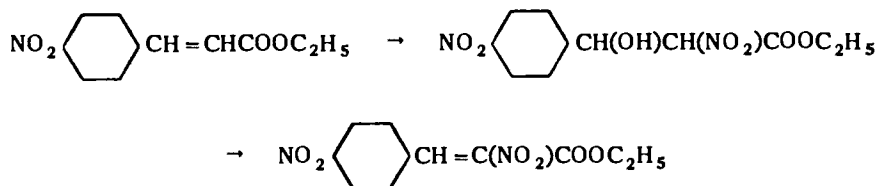
Many instances of the replacement of the carboxyl group with a nitro group during the nitration of phenolic acids have been noted.²⁰⁷ Replacement generally takes place the more readily the greater the number of hydroxyl, or other *ortho-para* directing group, attached to the nucleus, although 2,3,4-trimethoxybenzoic acid gives only the normal nitration product. Nitration of anisic acid with a mixture of sulfuric and absolute nitric acid yields the normal mono nitro acid, as well as 2,4-dinitro- and 2,4,6-trinitroanisole.²⁰⁸ *Prehnitine carboxylic acid*, treated with a mixture of fuming nitric acid and sulfuric acid at 10°, is converted to dinitroprehnitine:²⁰⁹



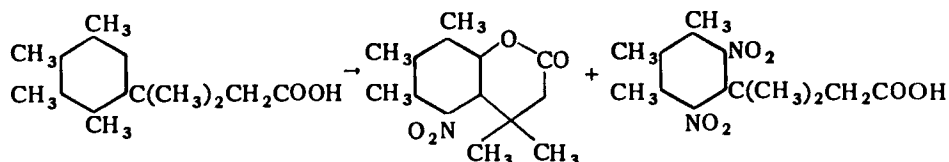
The nitration of *cinnamic acid* proceeds normally when ordinary concentrated nitric acid is employed, and results in the formation of *o*- and *p*-nitrocinnamic acid. When, however, nitric acid of density 1.52 (99.7% HNO₃) is used and the reaction is carried out at 0°, a mixture of β -2-dinitrostyrene and β -4-dinitrostyrene is obtained in 50 to 75% yield:²¹⁰



This behavior is shown also by *para* nitro-, -halo-, -amino-, and -methoxy cinnamic acids. The nitration of *ethyl p*-nitrocinnamate with absolute nitric acid at 0° results in the formation of β -4-dinitrocinnamic acid, with intermediate formation of a dinitrohydroxydihydrocinnamic acid:



Nitration of β -(1,3,4,5-trimethylphenyl)isovaleric acid or its methyl ester with a mixture of fuming nitric acid and sulfuric acid at 10° results in the formation of 4,4,6,7,8-pentamethyl-5-nitrohydrocoumarin, together with a dinitro acid, which would appear to be 2,6-dinitro- β -(3,4,5-trimethylphenyl)isovaleric acid:²¹¹



Nitration of Amines

Nitric acid is capable of attacking aromatic amines causing their oxidative breakdown. It is therefore necessary, in nitrating these substances, to take measures to prevent the oxidation of the amino compound. The presence of nitrous acid is undesirable when nitrating primary amines, since these substances are rapidly converted to diazo compounds by nitrous acid. It is important, therefore, to use nitric acid free from nitrous acid when nitrating aromatic amines.

The amino group may be protected from the oxidative action of nitric acid by carrying out the nitration in the presence of a large excess of sulfuric acid, which combines with the amine to form a salt. The reaction is preferably carried out at a low temperature. Nitration of amines in sulfuric acid generally leads to the formation of *meta* nitro derivatives.²¹²

p-Toluidine, nitrated in this manner, gives 2-nitro-*p*-toluidine; *o*-toluidine gives 75% of 4-nitro-*o*-toluidine, together with 20% of the 6-nitro and 3% of the 5-nitro isomers.²¹³ *o*-Chloroaniline, nitrated by this method, gives exclusively the 4-nitro derivative; *m*-chloroaniline yields 59% of the 6-nitro, 39% of the 4-nitro, and 2% of the 5-nitro derivatives, while *p*-chloroaniline gives 98% of the 3-nitro and 2% of the 2-nitro compound.²¹⁴

Picramide, or 2,4,6-trinitroaniline, may be prepared readily from *o*- and *p*-nitraniline by the action of a mixture of anhydrous sulfuric acid (sulfuric acid "monohydrate") and potassium nitrate.²¹⁵ *m*-Nitraniline is converted to 2,3,4,6-tetranitraniline by treatment with a mixture of concentrated sulfuric acid and an alkali nitrate at 70° for a few minutes.²¹⁶

3-Nitro-2-aminoanthraquinone has been obtained by nitrating 2-aminoanthraquinone in sulfuric acid monohydrate with the theoretical amount of nitric acid at a low temperature.²¹⁷

The amino group in aromatic bodies may be effectively protected by con-

version to an amido group by acylation. The derivative usually employed is the *acetylated amine*.

The *procedure* is to add the acetylated amine gradually to a mixture of fuming nitric acid and glacial acetic acid. The temperature is generally maintained at about 5° during the reaction in order to prevent any hydrolysis, and the formation of tarry matter. The mixture is agitated for a few hours, while the temperature is allowed to rise gradually to that of the surrounding atmosphere. The mixture is then poured on ice and the acylated nitroamine separated and dried. Removal of the acetyl group is effected by short boiling with aqueous acid or alkali. Occasionally a mixture of nitric and sulfuric acids is employed instead of one of fuming nitric and glacial acetic acid as the nitrating agent.

When the nitration of acetanilide with a mixture of nitric and glacial acetic acids is carried out in the presence of a little urea, the nitrated product consists of a mixture of the *ortho* and *para* nitro isomers in the ratio 3 to 1.²¹⁸ The *para* isomer is obtained as the principal product, if nitration is effected by adding fuming nitric acid at $10-20^{\circ}$ to a suspension of the acetanilide in two volumes of strong sulfuric acid and one volume of glacial acetic acid. It has been claimed that when the nitration of acetanilide is carried out with a mixture of nitric and sulfuric acids in the presence of an excess of sulfuric acid, the *para* nitro compound is obtained as the principal product, with only 2-5% of the *ortho* isomer. In the nitration of acetanilide with mixed acids, the yield of nitrated anilide decreases greatly when sulfuric acid of 80% concentration is used, and nitration fails to take place when 75% sulfuric acid is used.²¹⁹

A method of separation of *ortho* and *para* nitroacetanilides makes use of the solubility of the *para* isomer at 0° in a mixture consisting of 1 volume 50% aqueous potassium hydroxide, 1 volume alcohol, and 4 volumes of water.²²⁰

The nitration of the acetyl derivative of *p*-toluidine yields the 3-nitro derivative. 2-Nitroaceto-*p*-toluidide, nitrated at 0° in concentrated sulfuric acid by the addition of a mixture of anhydrous nitric acid and concentrated sulfuric acid gives the 2,3-dinitro derivative.²²¹ The 4- and 6-nitro compounds have been obtained through the nitration of aceto-*m*-toluidide with nitric acid of density 1.5 below 25° .³⁹⁴

Dinitro-*m*-toluenediamine has been prepared by nitrating the diacetyl derivative of *m*-toluenediamine, mixed with 20% urea, with a nitrating agent consisting of distilled nitric acid dissolved in six times its weight of sulfuric acid, nitration being effected in the temperature range $5-10^{\circ}$.²²²

p-Acetaminophenol, nitrated in sulfuric acid solution at -5° gives 2-nitro-4-acetaminophenol; but when the compound is treated directly with nitric acid at -5° , the 3-nitro derivative is formed. An ethoxy residue *ortho* to the acetamino group entirely prevents the entrance of the nitro group in *ortho* position and directs the latter to the *meta* position *ortho* to the ethoxy group.²²³

The acetyl derivative of *o*-chloroaniline, treated with nitric acid at -20° , gives 59% of the 4-nitro, 39% of the 6-nitro, and 2% of the 5-nitro derivative; acetylated *m*-chloroaniline yields 56% of the 4-nitro and 44% of the 6-nitro derivative, while acetylated *p*-chloroaniline gives solely the 2-nitro derivative.²¹⁴ The acetyl derivative of 6-chloro-*o*-toluidine yields the 3-nitro derivative.²²⁴

Nitration of *m*-acetaminobenzoic acid with concentrated nitric acid of density 1.54 results in the formation of two isomeric nitro-*m*-acetaminobenzoic acids, in both of which the nitro group is in *ortho* position to the acetamino group.²²⁵ On nitrating the compound in solution in sulfuric acid with the calculated amount of nitric acid, one-third of the acid is converted to the 3-acetamino-6-nitro derivative.²²⁶

Phenylacetanilide, or acetdiphenylamine, is converted to trinitrodiphenylamine when boiled with nitric acid of density 1.029; methylacetanilide gives dinitromethylaniline.²²⁷

The amino group may be protected by conversion into an *ethyl formamino* group, $-NHCOOC_2H_5$, by reaction with ethyl chlorocarbonate, $ClCOOC_2H_5$.

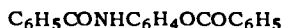
The compound obtained on nitrating the urethane may differ from that obtained on nitrating the acetamino derivative. For example, while 1-acetaminoanthraquinone gives the 4-nitro derivative, 1-(ethyl formamino)anthraquinone yields the 2-nitro derivative in considerable quantity, together with the 4-nitro compound.²²⁸ Also, the acetyl- or the oxalyl- derivative of 2-aminoanthraquinone give the 1-nitro derivative as the principal product, whereas the corresponding urethane gives the 1-nitro and 3-nitro derivatives.²²⁸ The nitro group first enters the *ortho* position with respect to the urethane residue.

The use of the *oxanilide* derived from the amine, rather than the acetanilide, may present an advantage.

Thus, in the preparation of *o*-nitraniline, it is preferable to employ the *oxanilide*, which is first converted to the disulfonic acid, and is subsequently nitrated. Hydrolysis of the nitrated product with dilute sulfuric acid gives *o*-nitraniline. The *oxanilide* is obtained by boiling for a few minutes a mixture of the oxalate of the amine with crude cresol boiling below 200°. ²²⁹

The amino group may be protected also by acylating with an aromatic acyl chloride. In compounds thus acylated, the nitro group is apt to attack the aromatic nucleus of the acyl group as well as that of the amine. As a rule, nitration of the arylamine residue takes place more readily than that of the acyl residue.²³⁰

p-Benzoylaminophenol, nitrated below 40° in sulfuric acid with mixed acids, is converted to 2,6-dinitro-4-benzoylaminophenol,²³¹ while the dibenzoyl derivative,



treated with nitric acid of density 1.52, first at room temperature, then allowing the temperature to rise to a maximum of 60°, is converted to dinitrodibenzoyl-*p*-aminodinitrophenol.²³² 2-Nitro-4-benzoylaminophenyl benzoate is formed when the dibenzoyl compound is treated at room temperature with nitric acid of density 1.48.

The *phthalanil* derived from aniline has been employed for the preparation of *p*-nitraniline by nitration in sulfuric acid solution at 0°. ²³³ The method presents the advantage that the resulting nitrophthalanil may be decomposed with aniline, thus regenerating phthalanil which may be employed for further nitration. The 2,4-dinitro compound is obtained by using the amount of nitric acid required for dinitration.

Diacylation of a primary amino compound, i.e., replacement of both hydrogen atoms attached to the nitrogen atom by acyl residues, protects the amino group completely.

Amino groups in aromatic compounds may be protected, further, from the oxidative action of nitric acid, by conversion to a *sulfanylamide* group by reaction with a sulfonyl chloride. *p*-Toluenesulfonyl derivatives have been found useful for the purpose. These derivatives are especially suitable for the preparation of dinitrated amines. Nitration of toluenesulfonyl derivatives of amines is usually carried out with nitric acid alone, or with a mixture of nitric and glacial acetic acids. The use of a mixture of nitric and sulfuric acid causes nitration to proceed further, and also induces the entrance of a nitro group into the toluene nucleus.²³⁴ A single isomer is obtained if the reaction is carried out in an appropriate solvent, such as methyl or ethyl alcohol, acetone, benzene, etc.

p-Toluenesulfanilide, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHC}_6\text{H}_5$, has been converted to the *o,p*-dinitro

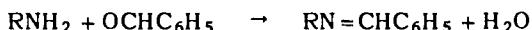
derivative by treatment with 55% nitric acid, the acid attacking the aromatic group bearing the amino group.²³⁵ *p*-Toluenesulfon-*o*-toluidide can be converted to a mono nitro derivative by stirring with 20% nitric acid for three or four hours at 60-70°. The dinitro derivative is formed at higher temperatures.²³⁶ The dinitro compound is obtained more readily by nitrating the sulfontoluidide at 50° with a mixture of fuming nitric acid and glacial acetic acid. The temperature should not be allowed to exceed 50° during the reaction, since otherwise, the reaction tends to become violent.²³⁷ The *p*-toluenesulfonyl derivative of *p*-anisidine gives the 3-nitro-*p*-anisidine derivative on treatment with nitric acid of density 1.4 in acetic acid solution at 22°.²³⁴ The *p*-toluenesulfonyl derivative of 1-amino-6-chlorotoluene gives on nitration the 5-nitro derivative, in contrast to the acetyl derivative, which gives the 3-nitro derivative.²²⁴

The *phenacyl group*, $C_6H_5COCH_2$, has been used for the protection of amino groups in aromatic compounds during nitration. Phenacyl-*p*-toluidine,



has been converted to its 3-aminonitroderivative, $C_6H_5COCH_2NHC_6H_3(CH_3)NO_2$, by treatment with 22% nitric acid; the dinitro derivative is obtained on treatment with 65% nitric acid.²³⁸

Amino groups in aromatic compounds may also be protected from the oxidative action of nitric acid by forming their condensation product with benzaldehyde:



Condensation is effected simply by warming the amine with benzaldehyde. The benzylidene derivative formed separates as an oily layer and settles to the bottom of the reaction vessel. It is separated, dissolved in strong sulfuric acid, and nitrated at 5-10° with a mixture of nitric and sulfuric acids. Upon completion of the reaction, the mixture is poured into an equal volume of water, and the whole subjected to steam distillation, whereupon the nitrated benzylidene derivative is converted to the nitrated amine and benzaldehyde, the latter passing over with the steam. On cooling the residue and diluting it with water, the greater part of the nitrated amine separates out. The remainder is recovered by neutralizing the acid with caustic. Nitration proceeds without the formation of resinous matter. The product is free from the ortho nitro isomer, and is obtained in 90% yield.²³⁹

The condensation of the amino group with formaldehyde has also been employed as a method of protection for the amino group. The method has been used for the preparation of nitrated derivatives of aminoanthraquinones.²⁴⁰

The amino group in aromatic amines has also been protected by condensation with purpurin, or 1,2,4-trihydroxyanthraquinone.

Another method employed for the protection of amino groups is their conversion to a nitroamino group, $-NHNO_2$, by treatment with nitric acid of density 1.5 to 1.52. This method is particularly useful in the anthraquinone series. After nitration of the nitramine, the amino group may be readily regenerated by agitating the compound with sulfuric acid, or by heating it under pressure with ammonia.

Nitration of *N*-Alkylated Amines

N-Alkylated aromatic amines can be successfully nitrated with a mixture of nitric and sulfuric acids.

Dimethylaniline, for example, may be nitrated in the following manner:²⁴¹ The amine

is dissolved in a large excess of concentrated sulfuric acid with cooling, and a mixture of fuming nitric acid with about five times its volume of sulfuric acid is added gradually while the temperature is maintained between 0° and 4° . The mixture is then poured on ice and diluted with a large volume of water, whereupon the nitrated compound separates out. The product consists of a mixture of the *meta* and *para* nitro derivatives in nearly equal amounts. The *meta* isomer may be separated from the *para* nitro derivative by partial precipitation from an aqueous solution of the sulfates of the two isomers, by the addition of caustic just sufficient to decompose one isomer.

3-Nitrodimethylaniline may be further nitrated to 3,6-dinitrodimethylaniline, and this, in turn, may be converted to 3,4,6-trinitrodimethylaniline. This compound, treated with one molecular equivalent of nitric acid, is converted to 2,3,4,6-tetranitrodimethylaniline, which with boiling nitric acid gives 2,3,4,6-tetranitrophenylmethylnitramine.²⁴² If the nitration of dimethylaniline is carried out in strong sulfuric acid, by use of a large excess of fuming nitric acid, say $7\frac{1}{2}$ moles per mole of the base, at 40° , and the mixture is then heated to 55° , "tetryl", or 2,4,6-trinitrophenylmethylnitramine, is obtained.²⁴³ One nitro group in this compound is attached to the nitrogen of the amino group.

Dimethylaniline, treated with a mixture of cupric nitrate and acetic anhydride below 50° , gives trinitrophenylnitramine.

Vigorous nitration of alkylated aromatic amines results in the formation of alkyl nitramines with loss of one alkyl residue from the amino group.²⁴⁴

The position of entrance of the nitro group into the aromatic group may be influenced by the concentration of sulfuric acid used as a solvent. For example, when *p*-chlorodimethylaniline is nitrated in solution in 97% sulfuric acid, the product is 3-nitro-4-chlorodimethylaniline, whereas, if the nitration is carried out in 70% sulfuric acid, the product is almost pure 2-nitro-4-chlorodimethylaniline.²⁴⁵

On nitration of *para*-substituted N-dialkylamines, the nitro group enters the *ortho* position to the dimethylamino group.²⁴⁶ *p*-Chlorodimethylamine forms an exception, and yields the *meta* nitro derivative. *N*-*n*-butyl-*p*-toluidine, nitrated with a molecular proportion of nitric acid in concentrated sulfuric acid, is converted to 2-nitro-4-butylaminotoluene, whereas the acetylated amine, treated similarly, gives the 3-nitro compound.²⁴⁷ Vigorous nitration of the 2-nitro derivative gives the 2,3,5-trinitro compound.

Diphenylamine, treated with a mixture of cupric nitrate and acetic anhydride below 50° , gives hexanitrodiphenylamine.²⁴⁸

Mono- and di-N-alkylated aminoanthraquinones may be nitrated with nitric acid of various concentrations, or in acetic acid solution with a variety of nitrating agents. The di-N-alkylated derivatives are converted to mono-N-alkylated nitro compounds by the treatment.²⁴⁹

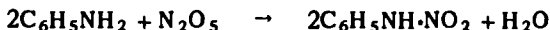
α -Alkylaminoanthraquinones are converted to their 5-nitro derivatives by nitrating their acylated derivatives in solution in sulfuric acid with a mixed acid of 27% nitric acid content, and subsequently saponifying the resulting acylated nitro compound.²⁵⁰

Certain N-alkylated aromatic amines have been nitrated by use of *nitrous acid*. 3-Nitro-4-dimethylaminotoluene has been obtained in 80% yield by the action of nitrous acid on dimethyl-*p*-toluidine.²⁵¹ Nitric acid of equal concentration is without action on the compound. N-Dimethyl-*p*-anisidine has been similarly converted to 3-nitro-4-dimethylaminoanisole in 91% yield,²⁵² and dimethylaminoacetanilide has been converted to a 3-nitro derivative by this method in 100% yield.²⁵³ *p*-Chlorodimethylaniline, treated with nitrous acid, gives 2-nitro-4-

chlorodimethylaniline, while treatment with nitric acid gives the 3-nitro derivative.²⁴⁶ Nitrous acid does not effect the nitration of dimethylaniline derivatives with an *ortho* substituent.²⁵⁴

Nitramines

Aromatic nitramines are formed through the reaction of nitric anhydride with amines:²⁵⁵



The yield of the nitramine obtained depends on the stability of the product. *p*-Toluidine has been converted to the corresponding nitramine by heating with a 10% solution of nitrogen pentoxide in carbon tetrachloride. 2,4-Dichloroacetanilide is not affected on treatment with nitrogen pentoxide. Aminoanthraquinones are converted to nitramines on treatment with nitric acid of density 1.50 to 1.52. A few secondary aromatic amines give the corresponding nitramines in excellent yield when treated with benzoyl nitrate.⁴⁴ Nitramines may be obtained in the form of their sodio derivative from aniline and its homologs by the action of ethyl nitrate in the presence of sodium ethylate in ethereal alcoholic solution.²⁵⁶

Diphenylamine, treated with nitrous acid in ethereal solution, gives diphenylnitrosamine; in benzene solution, *p*-nitrodiphenylamine is first formed, and is converted to *p*-nitrodiphenylnitrosamine.²⁵⁷

Aromatic nitramines isomerize under the action of mineral acids. Thus, *o*- and *p*-nitranilines result when phenylnitramine, $\text{C}_6\text{H}_5\text{NHNO}_2$, is treated with a mixture of concentrated sulfuric acid and acetic acid; *o*-nitrophenylnitramine gives 2,6-dinitroaniline.²⁵⁸ Anthraquinonenitramines are converted to aminonitroanthraquinones by treatment with concentrated sulfuric or hydrochloric acid.²⁵⁹ Other reactions usually accompany the migration of the nitro group. Small quantities of diazonium salts are formed, especially from halogenated nitramines. Thus, 2,4,6-trichloro- and 2,4,6-tribromophenylnitramines yield, in addition to the normal product of the rearrangement, some diazonium salt. Halogenated quinoneanils are also formed in small quantities from these compounds. The tribromo compound also yields some 2,6-dibromo-4-nitraniline through the elimination of one bromine atom.²⁶⁰

Nitration of Aromatic Halo and Sulfonic Compounds

Halogenated compounds are usually nitrated by methods similar to those employed for the nitration of hydrocarbons.

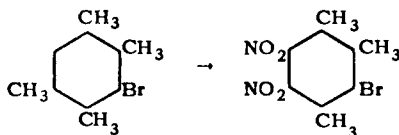
Chlorobenzene, is readily nitrated with a molecular equivalent of nitric acid at a comparatively low temperature, giving a mixture of *o*- and *p*-nitrochlorobenzene with a small amount of the *meta* isomer. With a greater amount of nitric acid and under more drastic conditions, 2,4-dinitrochlorobenzene is formed as the principal product. Chlorobenzene has been nitrated with a molecular equivalent of liquid nitrogen peroxide, N_2O_4 , in the presence of a molecular equivalent of aluminum chloride at -12 to -5° . Nitration proceeds smoothly and is complete within one hour. Upon completion of the reaction, the mixture is poured in ice, and the product is isolated by filtration. The nitrated product consists of 77% of the *para* compound and 23% of the *ortho* isomer. Bromobenzene, treated in the same manner, gives a product consisting of 94% of the *para* nitro derivative and 6% of the *ortho* nitro derivative. Nitrochlorobenzene is formed in high yield when a mix-

ture of chlorobenzene and sodium nitrite is added gradually to 65-90% sulfuric acid heated to 70-250°. ²⁶¹

2,4-Dinitro-1-chlorobenzene, treated with 8 parts of a 1:6 mixture of 90% nitric acid and 100% sulfuric acid at 130°, gives picryl chloride in 85% yield. ²⁶² Conversion to picryl chloride is also accomplished by heating the compound at 140-150° with mixed nitrating acids containing 40% of sulfur trioxide. ²⁶³ *m-Dichlorobenzene*, treated with mixed nitrating acids at water bath temperature, yields a mixture of 2,4- and 4,6-dinitro-1,3-dichlorobenzene. ²⁶⁴ *p-Dichlorobenzene*, treated similarly at boiling temperature, gives all of the three possible isomeric dinitro derivatives. ²⁶⁵ *o-Dichlorobenzene* gives 3,5-dinitro-1,2-dichloronitrobenzene, together with some of the 4,5-dinitro isomer. ²⁶⁶

4-Chlorotoluene, treated with "mixed acids", gives 2- and 3-nitro-4-chlorotoluene. ²⁶⁷

Bromodurene, treated with fuming nitric acid, is converted to 3-bromo-5,6-dinitropseudocumene. ²⁶⁸



Chlorocymene has been nitrated to 2-chloro-5,6-dinitrocymene. ¹⁴⁸ In the nitration of chlorocymenes, the isopropyl group may be replaced with a nitro group. Replacement of the isopropyl group in some chlorocumenes during nitration has also been observed.

Nitration of α -chloro- or α -bromonaphthalene occurs successively at positions 4, 5 and 8; ¹⁴⁸ nitration of β -chloro- and β -bromonaphthalene results in the formation of the 1,6,-8-trinitro derivative. ¹⁴⁹

Chlorophenols have been nitrated by treatment with a mixture of sodium nitrate and sulfuric acid. *m*-Chlorophenol has been converted to 6- and 4-nitro-3-chlorophenol. Treatment with the above mixture, following treatment with oleum results in the formation of the 2-nitro derivative. ²⁶⁹ Further nitration of these compounds leads to the formation of 2,4- and 2,6-dinitrochlorophenol. The direct vigorous nitration of *m*-chlorophenol gives the 2,4- and 2,6-dinitro derivatives. Further nitration results in the formation of 2,4,6-trinitro-3-chlorophenol. When *m*-chlorophenol is first sulfonated with concentrated sulfuric acid, and then exhaustively nitrated and the resulting nitrated sulfonic acid is hydrolyzed, it gives 2,5,6-trinitro-3-chlorophenol.

Treatment of 2,4,6-tribromoaniline with fuming nitric acid dissolved in glacial acetic acid results in the formation of 2,6-dibromo-4-nitroaniline.

The behavior of *aromatic sulfonic acids* upon treatment with nitrating agents is similar to that of aromatic carboxylic acids. Nitration takes place with moderate ease, but requires the use of more powerful nitrating agents than the nitration of phenols and amines. The sulfonic group generally directs the nitro group to the *meta* position, although considerable amounts of *ortho* and *para* isomers are also often formed.

In the nitration of *benzenesulfonic acid* at 90-100°, a mixture of the three isomeric nitrosulfonic acids are obtained, the *ortho* isomer forming 32% of the total, and the *para* isomer 13%. The *ortho* nitro compound may be readily separated from the *meta* and *para* nitro derivatives by taking advantage of the greater solubility of its magnesium salt. ²⁷⁰

In the nitration of *naphthalenesulfonic acids*, ³⁹⁵ the α -position of the non-

sulfonated ring is attacked preferentially. If a sulfo group is present in each ring, the entering nitro group tends to attach itself to an α -position not *ortho* or *para* to the sulfonic group. If such a position is not available, mixtures of various isomeric nitro compounds are formed; the nitro group then enters an α -position *para* to the sulfonic group and a β -position *meta* to this group.

1,8-Dinitronaphthalene-3-sulfonic acid has been obtained by allowing mixed nitrating acids to react at 0 to -10° for a few hours with naphthalenesulfonic acid in solution in concentrated sulfuric acid, then finishing the nitration with an additional quantity of mixed acids at a maximum temperature of 10° .²⁷¹ β -Nitronaphthalenedisulfonic acid is obtained by treating a sulfuric acid suspension of 1,5-naphthalenedisulfonic acid at 0° with "mixed acids" containing the required quantity of nitric acid.²⁷² 8-Nitro-1,4-naphthalenedisulfonic acid has been obtained by treating a suspension of 1,4-naphthalenedisulfonic acid in concentrated sulfuric acid with "mixed acids" at 10 - 15° for a few hours.²⁷³

In the nitration of phenolsulfonic acids, the sulfonic group may be replaced with a nitro group.³⁹⁶ In general a position *ortho* or *para* to the hydroxyl group is nitrated before a sulfo group is replaced. The nitration of tyrosine-3-sulfonic acid in sulfuric acid solution results in the formation of 3,5-dinitrotyrosine.³⁹⁷

The action of nitrogen oxides upon *p*-chloro-, *p*-bromo-, and *p*-iodobenzenesulfonic acids causes the formation of corresponding halo nitro compounds by replacement of the sulfonic group.³⁹⁸

The isopropyl group in 2-methyl-5-isopropylbenzene sulfonic acid is replaced during the nitration of the latter.³⁹⁹

The nitration of alizarin α - and β -sulfonic acids takes place more readily when *nitrous acid* is employed as the nitrating agent rather than nitric acid.²⁷²

Nitration proceeds smoothly, for example, when 50 parts of sodium alizarin- β -sulfonate are dissolved in 100 parts of water by gentle heating, 200 parts of acetic acid are introduced, the temperature is brought to 40° , and 25 parts of sodium nitrite are added with good agitation.²⁷⁴

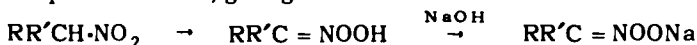
Aromatic sulfonyl chlorides are capable of undergoing nitration. 1,4-Diisopropylbenzene-2-sulfonyl chloride, for example, has been converted to 4-nitroisopropylbenzene-2-sulfonyl chloride by the action of a large excess of 96% nitric acid at 0 to 5° .

While the nitro derivative of β -naphthalenesulfonyl chloride may be obtained readily, the preparation of nitrated α -naphthalenesulfonyl chloride presents some difficulty. Satisfactory results are obtained when 1 part of the finely ground sulfonyl chloride is added to 3 parts of red fuming nitric acid of density 1.475 cooled to -5° . The sulfonyl chloride is introduced at such a rate that the addition of the total amount requires from 30 to 40 minutes. The mixture is well agitated during the addition of the chloride, and stirring is continued for one hour after the introduction of all the chloride. The mass is then poured on ice in a thin stream with stirring, and the solid which separates is filtered. It is rubbed with sodium carbonate solution, washed with water, and dried under reduced pressure.

A series of nitrated derivatives of *p*-substituted arylsulfamides have been prepared by nitration of the sulfamides in alcoholic solution.²⁷⁶

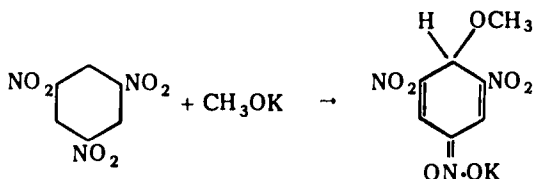
Behavior of Aromatic Nitro Compounds

Nitro groups attached to a secondary or tertiary carbon atom tend to isomerize to iso nitro groups; for this reason, compounds of the type $RR'CHNO_2$ or RCH_2NO_2 dissolve in aqueous caustic, giving the alkali metal salts of isonitro compounds:

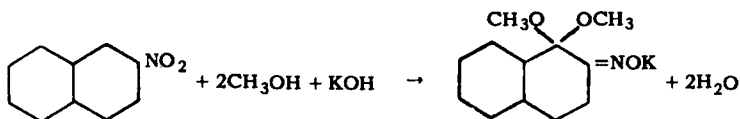


When solutions of alkali metal salts of isonitro compounds are treated with acid, the free isonitro compounds are obtained. The free isonitro compounds of the purely aliphatic series are unstable and cannot be isolated, but isonitro compounds of the type $RR'C = NOOH$, in which at least one of the groups R and R' is aromatic, are sufficiently stable to be isolated in the pure form.²⁷⁷

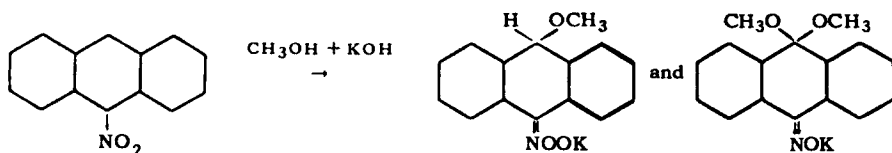
A similar isomerization is observed with certain aromatic nitro compounds in which a hydrogen atom is present in *ortho* or *para* position to the nitro group. Such compounds react additively with sodium alcoholates giving derivatives of isonitro compounds:²⁷⁸



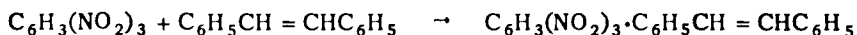
While α -nitronaphthalene does not react with methyl alcoholic potassium hydroxide, the β -nitro compound readily reacts to give an isonitroso derivative:²⁷⁹



α -Nitroanthracene gives both an isonitro and an isonitroso derivative:²⁸⁰



Certain nitrated aromatic bodies, among them nitrobenzene and nitrotoluene, have the ability to form well-defined compounds with sulfuric acid.²⁸¹ These compounds have a salt-like character. Nitrated aromatic bodies are also capable of forming addition products with unsaturated and aromatic compounds. An addition product is obtained, for example, through the interaction of trinitrobenzene with stilbene:



Nitro groups attached to the aromatic phenols enhance the acidic character of the hydroxy group. The reverse is true of aromatic amines, and nitro groups in *ortho* and *para* positions decrease the basic strength of the amine.

Nitro groups present in aromatic carboxylic acids increase the ease of decarboxylation of these acids. Conversely, such groups tend to stabilize the nitramine group in aromatic nitramines.

The presence of nitro groups in aromatic bodies increases the resistance of these substances to attack by halogens and halogenating agents; for this reason, nitrated aromatic compounds are best halogenated in the presence of halogen carriers. It should be noted that halogenated aromatic bodies offer little resistance to nitration.

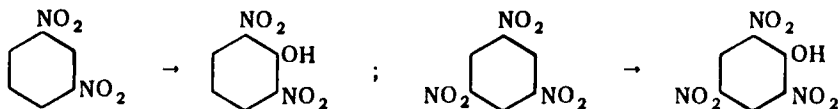
As a rule, nitrated phenols in which the nitro and hydroxyl groups are in *ortho* position to one another are more volatile than those in which these groups occupy *para* or *meta* positions. The *ortho* isomers are usually volatile with steam.

Aromatic nitro compounds are often attacked by hot concentrated sulfuric acid with ring rupture. *o*-Nitro-*p*-cresol, for example, is decomposed, on heating to 100° with 100% sulfuric acid, giving β -acetylacrylic acid, $\text{CH}_3\text{COCH}=\text{CHCOOH}$.²⁸²

Nitrated aromatic bodies are, in general, violent *poisons*. Quinine is recognized as a satisfactory antidote in cases of poisoning by such substances; it is also necessary to administer oxygen to the patient as soon as possible.²⁸³

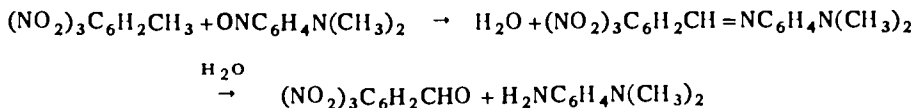
Activating Influence of Nitro Groups

Nitro groups in an aromatic nucleus activate *hydrogen atoms* situated in *ortho* or *para* position. The effect may be illustrated by the ready conversion of 1,3-dinitro and 1,3,5-trinitrobenzenes to phenolic bodies by oxidation:



The formation of amino nitro compounds by the reaction of hydroxylamine with aromatic nitro compounds is also a result of this activating influence.⁴⁰⁰ The amino group enters the *ortho* and *para* positions to the nitro group.

Nitro groups also activate methyl groups attached to the aromatic nucleus in *ortho* or *para* position to the nitro group. Methyl groups thus activated are capable of condensing with aldehydes. Thus, 2-methyl-5-nitrobenzonitrile, reacting with benzaldehyde in the presence of pyridine at 130-140° for one half hour, gives 2-cyano-4-nitrostilbene.²⁸⁴ The reactivity of the methyl group also manifests itself in the ability of this group to react with nitroso compounds. 2,4,6-Trinitrotoluene, for example, reacts with nitrosodimethylaniline to form a trinitrobenzylidene derivative, hydrolysis of which with concentrated hydrochloric acid results in the formation of trinitrobenzaldehyde and *p*-aminodimethylaniline.²⁸⁵



The reaction offers a satisfactory method for the preparation of 2,4,6-trinitrobenzaldehyde. 2,4-Dinitrotoluene also undergoes this reaction.²⁸⁶ Activated methyl groups may be condensed with oxalic ester in the presence of sodium ethylate; hydrolysis takes place spontaneously during this condensation, and the product obtained is a nitrated phenylpyruvic acid.²⁸⁷

Chlorine and other halogen atoms in *ortho* or *para* position to the nitro group are also activated and may be replaced with hydroxyl, alkoxyl, thiol, amino residues, etc.²⁸⁸ The reactivity of halogens decreases in the order bromine, chlorine, iodine. Halogen atoms in *meta* position to two nitro groups, as in 3,5-dinitrochlorobenzene, are not reactive.²⁸⁹ Replacement of reactive halogen atoms with hydroxyl may be brought about by heating with caustic solution or sodium alcoholates, and decomposing the resulting sodio derivative of the hydroxy compound with acid. Replacement with alkoxy groups may be accomplished by heating with the appropriate alcohol in the presence of some caustic.²⁹⁰ Alkoxy groups may, in turn, be replaced with amino groups by reaction with ammonia, or amines. Such a replacement has been effected, for example, with 2,4,6-trinitroanisole.²⁹¹ A highly reactive halogen atom, such as that in 2,4-dinitrochlorobenzene, may be replaced with a phenoxy group by heating with phenol in the presence of sodium ethoxide.²⁹² Replacement with a thiol group is effected by reaction with the sodium derivative of the thiol.²⁹³ Replacement with an amino group is brought about by heating with ammonia or an amine, under pressure if necessary.²⁹⁴ Replacement with the dimethylamine residue has been accomplished by refluxing the chloronitro compound with dimethylamine.²⁹⁵ The chlorine atom in 2,4-dinitrochlorobenzene may be readily replaced with the phenylhydrazine group. 2,4,6-Trinitrohalobenzenes react very readily with aniline, and less readily with its salts.²⁹⁶ Reaction with methylaniline takes place less readily than with aniline. Halogens in polynitrohalo compounds may be exchanged for an amino group by heating with urea at 130-135° in open vessels.²⁹⁷

The activating influence of nitro groups on halogen atoms is observed also in the *naphthalene* series. The chlorine in 1,3-dinitro-4-chloronaphthalene is reactive and may be replaced with various negative residues.²⁹⁸ The influence of a nitro group in producing a higher reactivity in a halogen atom does not extend from one ring to the other in the naphthalene nucleus.²⁹⁹

Nitro groups present in *ortho* or *para* position in benzyl chloride or its analogs also influence the reactivity of the chlorine atom attached to the methyl group. 2,4-Dinitrobenzyl chloride, for example, reacts readily with pyridine to form 2,4-dinitrobenzylpyridinium chloride.³⁰⁰

The activating influence of nitro groups in polynitro compounds is exerted also on nitro groups in *ortho* or *para* position. Nitro groups thus activated are replaceable by amino, alkoxy, and other residues.³⁰¹ One nitro group in *sym*-trinitrobenzene is replaceable with a methoxy group by treatment with cold methanolic sodium methylate.³⁰² Replacement of a nitro group in tetranitro compounds takes place with exceptional ease.³⁰³ It is sufficient, for example, to heat 2,3,4,6-tetranitroaniline with acetone containing a little water to convert

it to trinitroaminophenol.³⁰⁴ Normally, a labile nitro group may be replaced with an ethoxy group by heating with alcoholic potassium hydroxide; with a hydroxyl group by boiling with aqueous caustic; and with amino groups by heating with amines. The nitro group may be replaced also with hydrazine, hydroxylamine, semicarbazide groups, and other similar residues. The mobility of a nitro group is enhanced if it is flanked by two nitro groups, or is *para* to one nitro group and *ortho* to another.

The 3-nitro group in 2,3-dinitrochlorobenzene and the 4-nitro group in 3,4-dinitrochlorobenzene are the more labile; in 2,5-dinitrochlorobenzene the 2-nitro group is the more reactive. In 3,4-dinitrobromobenzene the 3-nitro group is the more labile,³⁰⁶ and the same is true of 3,4-dinitroanisole.³⁰⁷ In 2,3-, 2,5-, and 3,4-dinitrotoluene the nitro groups closer to the methyl group are replaceable.^{307 308} In 2,3,4-trinitrotoluene, the 3-nitro group is the more labile; the labile group in the 3,4,5-trinitro isomer is the 4-nitro group; and in the 2,3,5-trinitro compound the 2-nitro group.³⁰⁹ The nitro group in 4-position is labile in 2-chloro-4,5-dinitrobenzoic acid.³¹⁰

There are compounds that show an exceptional behavior. Thus:

3,5-Dinitrobenzoic acid is transformed to the sodium salt of 5-nitro-2,3-dihydroxybenzoic acid when treated with 12 normal sodium hydroxide at 40°.³¹¹

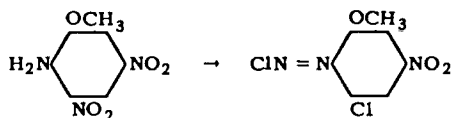
1,3,5-Trinitrobenzene is converted to tetranitroazoxybenzene when boiled with an aqueous sodium carbonate solution.³¹² 1,2,4-Trinitrobenzene gives under the same conditions 2,4-dinitroazoxybenzene.³¹³

3,4,6-Trinitro-1-chlorobenzene, treated with cold methanolic sodium methylate solution, gives 4,6-dinitroresorcinol dimethyl ether.³¹⁴

One *ortho* nitro group in 2,4,6-trinitrobenzaldehyde is partially replaced in the reaction of the compound with aniline.³¹⁵

2,4,6-Trinitroanisole and 2,4,6-trinitrometacresol methyl ether do not exchange any nitro group with organic bases, but the alkoxy group in these compounds is replaced with a basic residue.

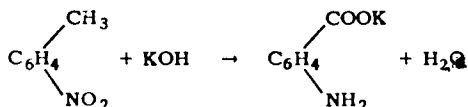
Diazotization of dinitro-*o*- or -*p*-anisidine in hydrochloric acid solution proceeds with the replacement of a nitro group in *ortho* position to the amino group with chlorine:³¹⁶



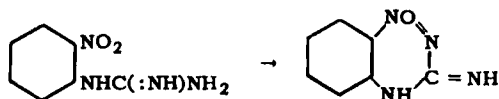
The labile nitro groups are replaced with hydroxyl groups when the diazotization is carried out in acetic acid solution.

Aromatic nitro compounds, boiled with alcoholic caustic or sodium ethylate, give

azoxy compounds, $\text{RN} \text{---} \text{O} \text{---} \text{NR}$. Resinous compounds also result from the aldehyde that forms during the reaction; their formation may be avoided by the addition of hydrazine.³¹⁷ Potassium anthranilate results when *o*-nitrotoluene is subjected to the action of potassium hydroxide in aqueous solution:³¹⁸



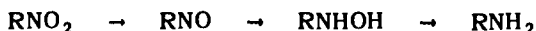
o-Nitrophenylguanidine, treated with potassium hydroxide, is converted to aminophentriazoxin;³¹⁹



o-Nitrophenylurea undergoes a similar transformation giving oxyphentriazoxin.

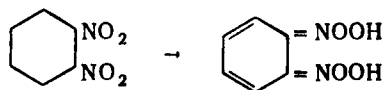
Reduction of Nitro Compounds

The reduction of nitro compounds proceeds according to Haber's rule,³²⁰ via the nitroso and hydroxylamine stages, to the amine:

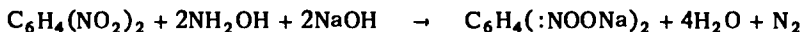


Azoxy compounds may be formed in the process by the condensation of the nitroso and hydroxylamine intermediates. The reduction may be effected by various methods. Among the most effective are those making use of metallic iron and water with a catalytic amount of hydrochloric acid, and of sodium sulfide. The subject has been considered in Chapter ~~27~~²⁶ dealing with aromatic amino compounds.

Ortho and *para* dinitrobenzenes may be converted to dinitro-dihydrobenzenes by careful reduction; the compounds probably exist in the isomeric quinoid isonitro form:³²¹



Conversion is accomplished quantitatively by use of hydroxylamine as the reducing agent:



The free diacidinitro compounds are not stable and rapidly decompose to a nitro-nitrosobenzene and a molecule of water.

Piria Reaction³²²

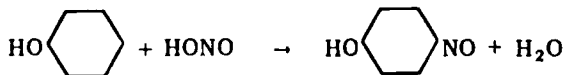
Treatment of a nitro compound with an aqueous solution of sodium bisulfite containing some sodium sulfite, at boiling temperature, results in the reduction of a small portion of the nitro compound to the corresponding amine. A larger proportion of sulfaminic acid is also formed, together with a varying amount of aminosulfonic acid. Hydrolysis of the sulfaminic acid with boiling dilute hydrochloric acid yields the amine. The total amine obtained under the best experimental conditions is somewhat over 80%. The reaction has been discovered by Piria and bears his name. A ring methyl group favors the formation of amines, whereas a carboxyl group, a second nitro group, and a condensed ring, favor the formation of aminosulfonic acids.

AROMATIC NITROSO COMPOUNDS

Methods of Preparation

Direct Introduction of the Nitroso Group into the Aromatic Nucleus

Direct nitrosation of aromatic compounds is possible only if hydroxy or amino groups are present in the nucleus. Nitrosation of *phenols* proceeds by the reaction of nitrous acid with phenols in aqueous or alcoholic solution. The nitroso group enters the *para* position to the hydroxyl group.³²³

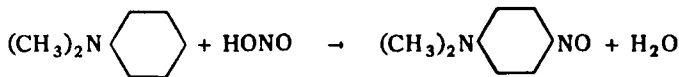


The reaction with phenol proceeds in aqueous solution at -10° . Monohydric phenols give mononitroso derivatives, while dihydric phenols, such as resorcinol, give dinitroso compounds. Substituted phenols, more particularly phenol-carboxylic acids, may also be nitrosated by this method. *p*-Nitrosohydroxy-carboxylic acids are also formed through the hydrolysis of *p*-nitrosoalkylamino-carboxylic acids.³²⁴ Naphthols are readily nitrosated with nitrous acid; α -naphthol gives 2- and 4-nitroso- α -naphthol, but β -naphthol yields only 1-nitroso- β -naphthol. 1-Hydroxy-2-naphthoic acid gives β -nitroso- α -naphthol with loss of carbon dioxide.

Direct nitrosation of phenols has been effected in special cases by use of *amyl nitrite*.

Mononitrosoresorcinol, for example, has been prepared in the following manner: A solution of 24 gm of potassium hydroxide in the minimum amount of water is added to one of 33 gm of resorcinol in 90 cc of alcohol; the mixture is cooled in a freezing mixture and 39 gm of amyl nitrite are added with agitation. The mixture is stored in an ice bath for 3 to 4 hours, whereupon the potassium salt of the nitrosoresorcinol formed precipitates out and is filtered, washed with alcohol and ether, and dried. The free nitrosoresorcinol is obtained by stirring 50 gm of the potassium salt in water, adding crushed ice, and acidifying with a mixture of 25 gm concentrated sulfuric acid with 75 gm water to which some ice has been added. The mononitrosoresorcinol precipitates out as a light yellow crystalline mass.³²⁵

Direct nitrosation of *tertiary aromatic amines*, like that of phenols, may be effected through the action of nitrous acid on the amine:



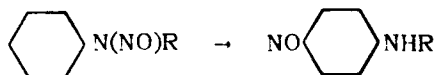
The procedure is to add sodium nitrite in excess to the aqueous solution of the hydrochloride of the base. If a substituent is present in the *ortho* position to the amino group, nitrosation does not take place, or takes a different course.³²⁶ Furthermore, nitrosation succeeds only if the alkyl groups attached to the amino nitrogen are of small molecular size.³²⁷ Many tertiary amines, reacting with nitrous acid, give a certain amount of nitrosamines by replacement of an N-alkyl

group by the nitroso group.³²⁸ Aromatic carboxylic acids containing a tertiary amino group may also be nitrosated with nitrous acid or with nitrosyl chloride.

Amines which contain an alkyl or alkoxy group in meta position to the amino group can be converted to *p*-nitrosoarylamines by dissolving in concentrated sulfuric acid and adding nitrous acid.³²⁹

Fischer-Hepp Rearrangement

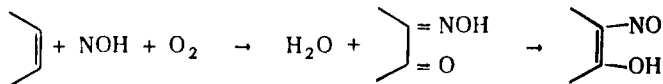
Nitrosoamines obtained through the reaction of nitrous acid with secondary aromatic amines may be transformed to nuclearly nitrosated amines by treatment at room temperature with alcoholic hydrogen chloride or hydrogen bromide:³³⁰



This is known as the *Fischer-Hepp rearrangement*. The transformation is not an intramolecular change, but involves the removal of the nitroso group by the halogen acid as nitrosyl halide, and the reaction of the latter with the amine.³³¹ The reaction is applicable, in addition to aralkylnitramines, to diaryl, alkyl-, aryl- α -naphthyl-, and alkyl- β -naphthyl nitramines. Dinitrosoamines derived from α,β -diphenylaminoethane and β,γ -diphenylaminobutanes also undergo the transformation. Concentrated hydrochloric acid, or a solution of hydrogen chloride in acetic acid, may bring about the transformation in cases where alcoholic hydrochloric acid fails to induce the change.³³² Nitrosoamines with a tertiary alkyl group attached to the amino nitrogen do not undergo the Fischer-Hepp rearrangement; when these compounds are subjected to the conditions intended to bring about the transformation, the nitroso group is eliminated.³³³ Treatment of nitrosoamines with sulfuric acid results in the decomposition of the nitrosoamine with regeneration of the amine. The reaction proceeds better in the presence of urea or thiourea.

Nitroso-Hydroxylation; The Baudisch Reaction

The nitroso group may be introduced into an aromatic compound simultaneously with a hydroxyl group through the reaction of the nitrosyl radical in the presence of an oxidizing agent:³³⁴



This is known as the Baudisch reaction. The nitrosyl radical is generated either by reducing nitrous acid or by oxidizing hydroxylamine. The presence of a copper salt is essential in this reaction to stabilize the nitrosyl radical, and to assure that an *ortho* nitrosophenol is formed, rather than a *para* nitroso derivative. The yield of *o*-nitrosophenol is relatively small. The method may be illustrated by the preparation of *o*-nitrosophenol from benzene:

Half a gram of freshly precipitated yellow cuprous hydroxide, CuOH , is suspended in 200 cc of distilled water containing half a gram of potassium nitrate in solution. Pure benzene is added to the mixture with good stirring, the pH is adjusted to 2.1 by the addition of the required amount of dilute hydrochloric acid, and 1 cc of 30% hydrogen peroxide is added. The deep red copper salt of the *o*-nitrosophenol is formed, from which the free *o*-nitrosophenol may be obtained by treatment with hydrochloric acid.

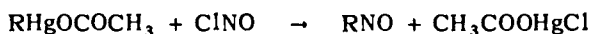
Treatment of hydroxylamine hydrochloride with cupric ions, and the reaction of hydrogen peroxide with benzenesulfohydroxamic acid in the presence of copper ions also generate nitrosyl radicals. A procedure adopted by Baudisch which has given satisfactory results is as follows:

Two grams of sodium pentacyano amine ferrate are dissolved in 100 cc distilled water, 25 cc of benzene and 50 cc of ligroin are added, the mixture is cooled in ice water, and 2 gm of sodium hydroxide and 4 cc of 30% aqueous hydrogen peroxide are added. The mixture is shaken well for one hour, and the benzene-ligroin layer is separated, washed with ice water, and extracted with aqueous copper sulfate, which dissolves the nitrosohydroxybenzene as the copper salt. The aqueous solution thus obtained is now acidified, and the free nitroso compound is extracted with petroleum ether and recovered from the solution by evaporation. This cycle of operations is repeated as long as the red color of the copper salt of the nitrosohydroxyphenol develops in the copper sulfate solution. Good yields of *o*-nitrosophenol have been obtained by this procedure.

The Baudisch reaction usually fails to take place with aromatic aldehydes and primary amines, the former giving hydroxamic acids, the latter diazo compounds instead of the expected hydroxy nitroso derivatives. The reaction is applicable to benzene and phenol derivatives with more than one substituent.

Exchange Reactions Leading to the Formation of Nitroso Compounds

Aromatic nitroso compounds are formed through the reaction of acetyloxymercury aryls with nitrosyl chloride:³³⁵



Nitrosobenzene has been obtained by the action of nitrosyl bromide on mercury diphenyl.³³⁶

Aromatic nitroso compounds may be prepared also through the reaction of aryl magnesium halides with nitrosyl chloride:³³⁷



Nitrosyl chloride is best prepared by distilling a mixture of nitrosulfonic acid and sodium chloride in a retort:



The compound boils at 2° . Nitrosulfonic acid is obtained by mixing concentrated sulfuric acid with red fuming nitric acid.

Nitroso Compounds by Oxidation of Aromatic Amines, Hydroxylamines, and Oximes

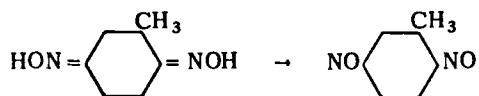
Aromatic amines may be converted to the corresponding nitroso compounds by use of certain oxidizing agents, such as sulfomonoperacid, or a mixture of po-

tassium bichromate and sulfuric acid.³³⁸ Oxidation apparently proceeds via the intermediate hydroxylamine:

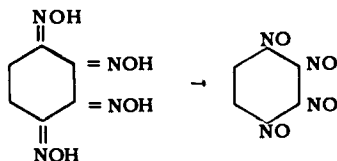


Aromatic nitroso acids have been prepared by the oxidation of the corresponding amino acids with Caro's reagent.³³⁹ Nitroso compounds may be prepared also by the oxidation of hydroxylamines with ferric chloride or chromic acid in cold aqueous solution. *o*-Hydroxylaminobenzoic ester has been converted to *o*-nitrosobenzoic acid by oxidation with potassium permanganate.³⁴⁰

Aromatic nitroso compounds have been obtained by oxidizing aromatic oximes. *p*-Dinitroso compounds have been prepared, for example, through the oxidation of *p*-quinone dioximes in alkaline solution with potassium ferricyanide:³⁴¹

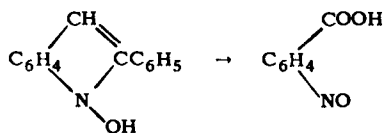


Oxidation of diquinoyltetroxime with sodium hypochlorite results in the formation of 1,2,3,4-tetranitrosobenzene:³⁴²



The conversion was accomplished by dissolving the tetroxime in fairly concentrated sodium carbonate solution, cooling the solution with ice, and adding a solution of sodium hypochlorite. An almost colorless, flocculent precipitate appears immediately and is filtered and washed with water.

o-Nitrosobenzoic acid results through the oxidation of phenyloxindole:³⁴³



Phenyloxindole is obtained from benzoic monoxime by removal of water.

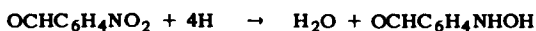
Nitroso compounds may be obtained by the action of benzenesulfonyl chloride on aromatic hydroxylamines.³⁴⁴

Nitroso Compounds by Reduction of Nitro Compounds

The reduction of aromatic nitro compounds to the corresponding hydroxylamine derivatives may be accomplished with zinc dust and acetic acid; oxidation of the hydroxylamine derivative to the nitroso derivative may be effected with ferric chloride or sulfomonoperacid. Nitrosobenzyl alcohols have been obtained by this method from the corresponding nitrobenzyl alcohols,³⁴⁵ and nitrosobenzaldehydes have been prepared similarly from nitrobenzaldehydes.³⁴⁶ Meta-dinitroso derivatives of aromatic hydrocarbons have been obtained by reduction

of *m*-dinitro derivatives by the same method, carrying out the reduction to the dihydroxylamino derivative at a low temperature.³⁴⁷ Oxidation of the hydroxylamino compound with ferric chloride may lead to the formation of the nitronitroso derivative.³⁴⁸

Meta and *para* nitrobenzaldehydes have been converted to the corresponding nitroso derivatives by reduction to the hydroxylamine derivatives and oxidation of the resulting nitrones with ferric chloride:⁴⁰¹

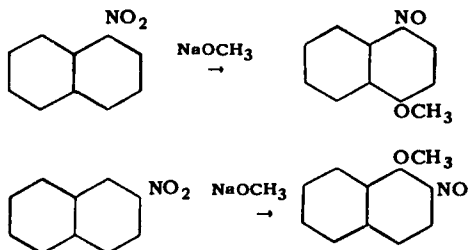


o-Nitrosobenzaldehyde cannot be prepared by this method. The compound has been obtained by the hydrolysis of *o*-aldehydenitrosophenylhydroxylamine with mineral acids:⁴⁰²

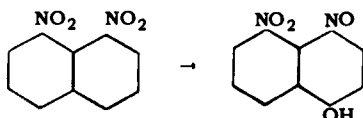


The compound is formed also by the oxidation of the nitroso hydroxylamine with potassium permanganate in acid or alkaline solution. Anthranil may be oxidized under certain conditions to *o*-nitrosobenzaldehyde.

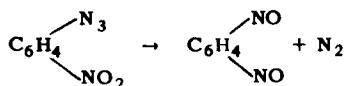
Nitronaphthalenes, treated with methanolic caustic, give the methyl ether of nitrosonaphthols:³⁴⁹



Nitrosonitronaphthols result on treating dinitronaphthalenes with fuming sulfuric acid:³⁵⁰

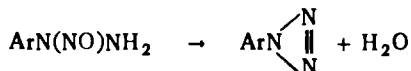


o-Dinitroso derivatives of benzene hydrocarbons are formed on warming *o*-nitrohydrazides:³⁵¹



N-Nitrosohydrazines and *N*-nitrosohydroxylamines result through the reaction of nitrous acid with hydrazines and hydroxylamines.³⁵² *N*-Nitrosohydrazines are

related to diazo compounds and readily change to diazoimides, i.e., arylazides, by dehydration:

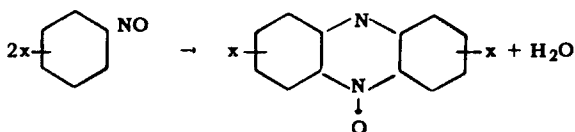


When *anti*-diazohydrates are dissolved in benzene or chloroform, they are immediately converted to nitrosoamines.

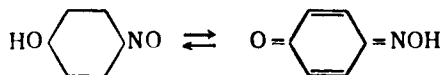
Behavior and Reactions of Aromatic Nitroso Compounds

Aromatic nitroso compounds, in common with their aliphatic counterparts, are white in the crystalline state, but become blue when liquefied or vaporized. Nitrosobenzene and its homologs in the solid state exist in the bimolecular form, but appear to undergo more or less complete dissociation when dissolved in a solvent, importing a blue color to the solution.³⁵³ If both positions ortho to the nitroso group are occupied by substituents, the dissociation is retarded.

Nitrobenzenes undergo dimerization of a different type under the influence of concentrated sulfuric acid; nitrosobenzene yields the compound $\text{C}_6\text{H}_5\text{N(OH)C}_6\text{H}_4\text{NO}$.³⁵⁴ If a *para* substituent is present in the compound, condensation may proceed partially with removal of this substituent.³⁵⁵ The principal product obtained, when halogenated nitrosobenzenes are condensed under the influence of sulfuric acid, are dihalophenazine oxides

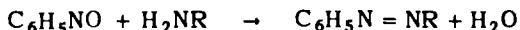


Nitrosophenols are tautomeric with quinone monoximes:



and the question whether they should be represented as derivatives of the phenolic or quinone form remains open.³⁵⁶ *p*-Nitrosophenol in ethereal solution seems to exist to the extent of about 70% in the quinoxime form.³⁵⁷ Hydroxylamine reacts with nitrosophenols and nitrosonaphthols to form the corresponding quinone dioximes. The alkylation of nitrosophenols and nitrosonaphthols results in the formation of quinone oxime ethers.³⁵⁸

Aromatic nitroso compounds react with primary amines to form azo bodies:³⁵⁹



Condensation with hydroxylamine in the presence of sodium carbonate leads to the formation of *syn* diazo compounds:³⁶⁰



Monoaryl hydrazines, ArNHNH_2 , reacting with aromatic nitroso compounds yield azohydroxylamines, $\text{ArN}=\text{N.N}(\text{OH})\text{Ar}'$,³⁶¹ while *asym* disubstituted hydrazines, ArN(R).NH_2 , give azo amine oxides, $\text{ArN(R)N}=\text{N.NAr}'$.³⁶²



A hydroxyl or amino group in *para* position to a nitroso group are labile and may be replaced with other negative groups; the hydroxyl with an amino group, for example, and vice versa. Thus, *p*-nitrosoamines have been converted to the corresponding nitrosophenols by boiling with aqueous alkalis,³⁶³ and nitroso-anthranilic acid has been obtained from 5-nitrosalicylic acid by fusing with a mixture of ammonium acetate or chloride, and a little ammonium carbonate.³⁶⁴

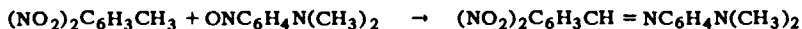
Reaction with Active Methylene – Ehrlich-Sachs Reaction

Aromatic nitroso compounds are capable of condensing with compounds containing a reactive methylene to form azomethines:³⁶⁵



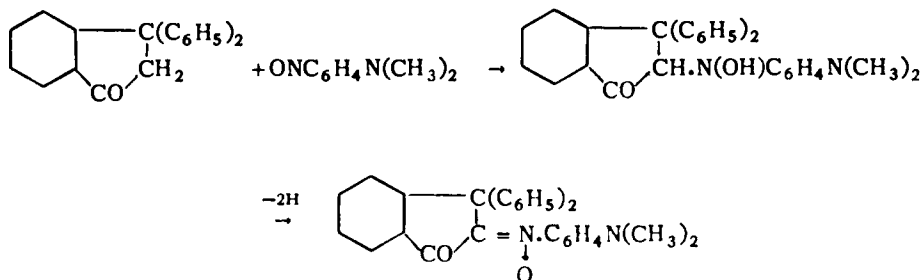
This is known as the Ehrlich and Sachs reaction. The condensation is usually carried out in alcoholic solution in the presence of alkalis or substances of basic nature, such as sodium carbonate, trisodium phosphate, or potassium cyanide. Organic bases, such as pyridine, are also effective condensing agents.

As an example may be cited the preparation of 2,4-dinitrobenzaldehydedimethylamino-anil, by reacting 2,4-dinitrotoluene with *p*-nitrosodimethylaniline in alcoholic solution in the presence of sodium carbonate. The reaction is completed by refluxing the mixture for five hours over a water bath:

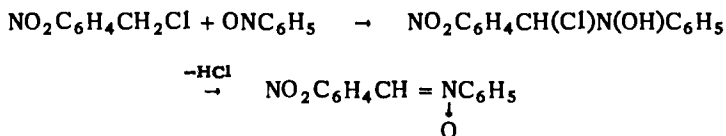


Successful condensation may be achieved in many instances only by carrying out the reaction in absolute alcoholic solution and using sodium ethylate or methylate as the condensing agent.³⁶⁶

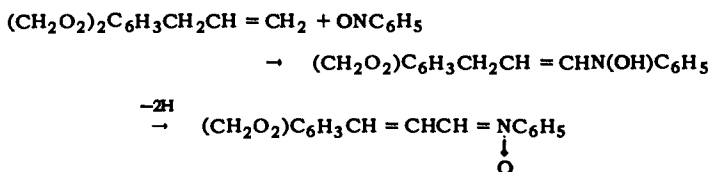
The reaction often results in the formation of degradation products of the expected azomethine;³⁶⁷ for example, phenylacetone, $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3$, reacting with nitrosodimethylaniline in the presence of alkali gives benzaldimethyl-*p*-phenylenediamine, $\text{C}_6\text{H}_5\text{CH}=\text{NC}_6\text{H}_4\text{N(CH}_3)_2$. Occasionally also *nitrones* are formed rather than the expected azomethines.³⁶⁸ *p*-Nitrosodimethylaniline, for example, gives a nitrone with 3,3-diphenyl-1-hydrindone:



Nitrones are formed also by the reaction of aromatic nitroso compounds with nitro compounds of the type of 2,4-dinitrotoluene.³⁶⁹ Nitrones result quite readily in the reaction of *p*-nitrobenzyl chloride with nitroso bodies:³⁷⁰



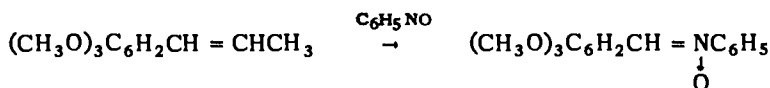
Safrole reacts with nitrosobenzene to give a nitrone:³⁷¹



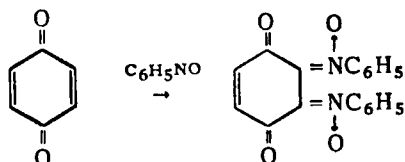
A portion of the nitrosobenzene is reduced, and the resulting phenylhydroxylamine condenses with some of the nitrosobenzene to form azoxybenzene.

Reaction with Unsaturated Compounds

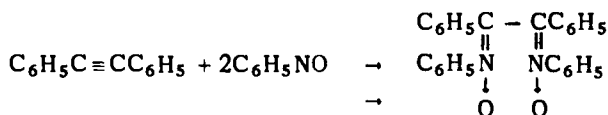
Compounds containing a carbon to carbon double bond react with nitroso compounds in different ways depending on the character of the compound. The reaction of safrole with nitrosobenzene has just been pointed out. *Asarone* reacts with nitrosobenzene giving a nitrone with loss of two carbon atoms:



Quinones react with aromatic nitroso compounds forming dinitrones:³⁷²

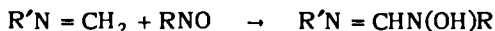


Nitrosobenzene is capable of adding at a triple bond to form a dinitrone,³⁷³ tolan, for example, gives with nitrosobenzene the diphenyldinitrone of benzil:



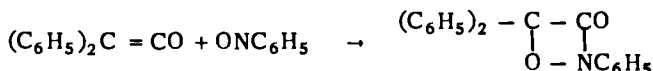
Propiolic acid behaves similarly. Styrene also gives a nitrone with nitrosobenzene.

Aromatic nitroso compounds react with Schiff bases of formaldehyde giving N-hydroxyformamidines:³⁷⁴

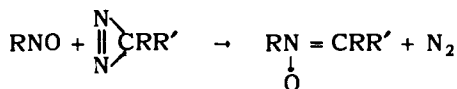


When these compounds are heated, they are converted to $R'N = C = NR$.

Nitrosobenzene reacts with diphenylketene to form a cyclic oxime:

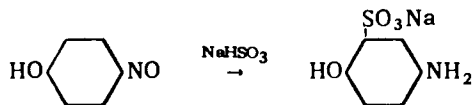


Nitrones result through the reaction of nitroso compounds with aliphatic diazo compounds:³⁷⁶

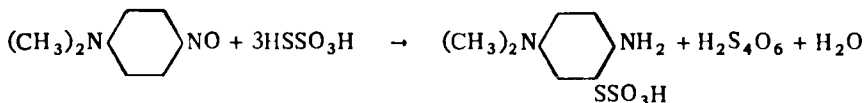


Reduction of Nitroso Compounds

Nitroso compounds may be converted to amines by reduction with stannous chloride or sodium sulfide.³⁷⁷ Reduction may also be effected by use of zinc or iron and hydrochloric acid. Nitroso amines, for example, may be converted to hydrazines by treatment with zinc dust and acetic acid. Nitrosoanilides are converted to the original amine, however, even with mild reducing agents. Sodium bisulfite causes the reduction of the nitroso group, and the entrance, simultaneously, of a sulfonic group into the nucleus:³⁷⁸



α -Nitroso- β -naphthol similarly gives 1-amino-2-naphthol-4-sulfonic acid,³⁷⁹ and β -nitroso- α -naphthol gives 1-hydroxy-2-aminonaphthalene-4-sulfonic acid.³⁸⁰ A similar reaction is observed with sodium thiosulfite reacting with a α -nitrosoamine in the presence of acetic acid or sodium acetate:³⁸¹



Benzenediazonium nitrate results on treating nitrosobenzene with nitric oxide in chloroform solution; the compound is formed also by the action of nitrous acid on nitrosobenzene dissolved in acetic acid.³⁸²

Oxidation of Aromatic Nitroso Compounds

Nitroso compounds may be oxidized to nitro bodies by treatment with nitric acid or certain other oxidizing agents. Nitrosophenols and nitrosonaphthols are effectively oxidized, as a rule, by treatment with nitric acid or alkaline potassium ferricyanide.³⁸³ Nitrosodimethylaniline has been converted to the corre-

Nitronitro body by treatment with alkaline potassium ferricyanide or potassium permanganate.⁶³ Nitronitroso compounds have been converted to the corresponding dinitro derivatives by treatment with ferric chloride and sulfomonoper acid or by heating with moderately dilute nitric acid (density 1.26).⁶⁴ The more resistant among nitronitroso bodies may give low yields by these treatments, but are effectively oxidized by use of a mixture of nitric acid and an acetic acid solution of hydrogen peroxide. Nitrosonaphthalene has been oxidized to nitronaphthalene by similar treatments. Nitrosodiphenylamine has been oxidized to nitrodiphenylamine by heating with ammoniacal hydrogen peroxide.³⁸⁴

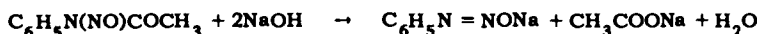
1,2,3,4-Tetranitrosobenzene shows great resistance to the action of hot concentrated nitric acid.³⁸⁵ Long boiling with this reagent causes deep seated decomposition, with the formation of a little 1,2,3,4-tetranitroso-6-nitrobenzene. *p*-Dinitrosobenzene, on the other hand, is readily converted to *p*-dinitrobenzene on gentle warming with fuming nitric acid.³⁸⁶

Behavior of Nitrosoamines

Aromatic nitrosoamines show a neutral reaction.³⁸⁷ They are generally stable toward dilute aqueous alkalis.

Nitrosoamines may be converted to the parent amine by removal of the nitroso group as nitrous acid by treatment with concentrated sulfuric acid. In order to prevent secondary reactions due to the liberated nitrous acid, some stannous chloride is added.³⁸⁸ Removal of the nitroso group may be effected also by heating with hydrochloric acid and alcohol, or zinc dust and hydrochloric acid. If nitro groups are present in the nucleus, removal of the nitroso group may be accomplished by heating with aqueous or alcoholic hydrochloric acid containing aniline hydrochloride, or by heating with phenol at 180°. Another method consists in adding an excess of a solution of cuprous chloride in concentrated hydrochloric acid to the nitrosoamines, and gently heating the mixture.³⁰⁵

Nitrosoacetanilide, treated at room temperature with aqueous sodium hydroxide, gives a sodium syn-diazotate:



Treatment with an aniline solution of β -naphthol results in the formation of an azo compound.²⁷⁵ Nitroso-*p*-bromoacetanilide and nitrosoacetnaphthalide behave in a similar manner. Aniline and phenol, reacting with nitrosoanilides, give diazo compounds.

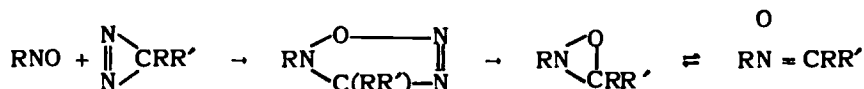
NITRONES AND NITRENES

Nitrones³⁷⁶ are compounds containing the grouping =NO- attached to a carbon atom. The nitrogen to oxygen bond in these compounds is semipolar in character. The first compounds of this type to be prepared have been obtained by alkylating aldoximes or ketoximes. They may be prepared also by the condensation of aldehydes or ketones with hydroxylamines:¹¹⁴

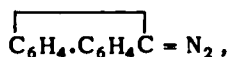


The compounds have been designated as aldonitrones or ketonitrones, depending on whether they are derived from aldehydes or ketones.

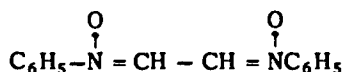
Nitrones are formed also through the reaction of nitroso bodies with aliphatic diazo compounds:



The ability of various diazo bodies to form nitrones varies greatly. Diazomethane, phenyldiazomethane, and phenylmethyldiazomethane react very readily; diphenyldiazomethane reacts less readily; diphenylenediazomethane,



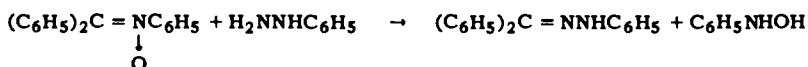
reacts still less readily, while diazomethane derivatives with two carbonvl groups, such as $\text{CH}_3\text{OCOC}(\text{:N}_2)\text{COC}_6\text{H}_5$, do not react at all. Only the true monomeric nitroso compounds are capable of undergoing the reaction. Diazomethane reacting with nitrosobenzene gives a dinitrone,⁶



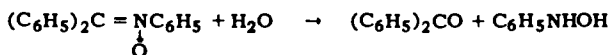
The formation of nitrones through the reaction of nitroso compounds with polynitrotoluenes, with quinones and unsaturated compounds has been pointed out in the section dealing with the reactions of nitroso compounds.

Aliphatically substituted nitrones appear to be unstable and polymerize rapidly.

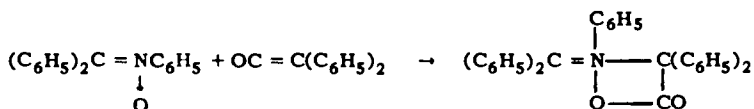
Phenyldiazine reacts with nitrones with liberation of an aromatic hydroxylamine and the formation of a phenyldiazine derivative:



Water reacts with nitrones with liberation of an aldehyde or ketone and the formation of an aromatic hydroxylamine:

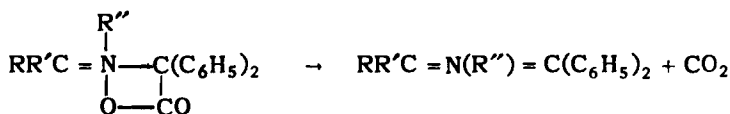


Diphenylketene reacts additively with nitrones forming a four-membered ring:



A second molecule of diphenylketene is capable of adding at the nitrogen to carbon double bond in the reaction product, forming a second four-membered ring.

Nitrenes are compounds containing the grouping $=\text{N}(\text{R})=$, joined to carbon atoms; they are obtained on heating the addition product of nitrones with diphenylketene:



The addition products of diphenylketene with diphenyl-N-methyl nitrene, with diphenyl-N-methylnitrene, and with benzophenone oxime failed to yield nitrenes.

Nitrenes combine with a molecule of hydrogen chloride forming an addition product which releases hydrogen chloride on heating, with regeneration of the original nitrene. The addition compound has a reactive chlorine replaceable with hydroxyl or other negative groups. Nitrenes add only one molecule of diphenylketene at one of the nitrogen to carbon double bonds.

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CHAPTER 30

AROMATIC SULFONIC ACIDS AND RELATED COMPOUNDS

SULFONIC ACIDS

Methods of Sulfonation

The process of replacement of a hydrogen atom in an organic compound with the sulfonic group, SO_3H , is termed sulfonation. Such replacement in aromatic bodies may be brought about by the action of concentrated or fuming sulfuric acid. Sulfonation may also be accomplished by means of a variety of other reagents; among these are chlorosulfonic acid, bisulfates, polysulfates, sulfites, bisulfites, and thionyl chloride. Sulfonation may be effected furthermore through the replacement of a substituent element or group by the sulfonic group.

The readiness with which aromatic compounds are sulfonated varies according to the character of the compound. Benzene may be sulfonated with sulfuric acid of a concentration in excess of 78.4%; naphthalene may be sulfonated with acid of 63.7% strength, and anthracene with 53% acid. The sulfonation with sulfuric acid may be greatly retarded by the water formed in the reaction.¹ The lower limit of concentration of sulfuric acid, expressed as percent sulfur trioxide, at which sulfonation can occur under a given set of conditions is defined as the π value of sulfonation.²

If the compound to be sulfonated may be distilled without decomposition, the water formed during sulfonation may be eliminated by refluxing the compound and returning it to the reaction flask after it has been separated from the water which distills over. This method may be employed with substances of low volatility by adding an inert moderately volatile liquid to the reaction mixture, and refluxing the latter. Carbon tetrachloride may be employed for the purpose in many instances.³

The majority of sulfonation reactions are carried out by the use of concentrated sulfuric acid or fuming sulfuric acid. Reaction may be brought about under atmospheric pressure in most cases. With the more resistant compounds, fuming sulfuric acid of high sulfur trioxide content is employed. Occasionally, it is necessary to resort to heating in a sealed tube under pressure.⁴ Concentrated sulfuric acid and fuming sulfuric acid exert an oxidizing action which is accentuated by a rise in temperature; for this reason it is desirable to work at the lowest possible temperature.

The sulfonic group preferentially enters the *ortho* position to a substituent,

if sulfonation is carried out at a low temperature, while at higher temperatures it enters the *para* position. A considerable proportion of the *para* sulfonic compound is formed at the lower temperatures however. It is not possible to protect the *para* position with intermediate substituents.

The sulfonic groups never enter positions *ortho*, *para*, or *peri* to one another in direct sulfonation reactions. This generalization is known as the *Armstrong and Wynne rule*. Exceptions to the rule have been observed in cases where other strongly directing substituents are present in the aromatic nucleus.

Sulfonation is rendered difficult if halogens, carboxyl, nitro, and sulfonic groups are attached to the aromatic nucleus. Dinitro derivatives of aromatic hydrocarbons cannot, in general, be sulfonated.

Among derivatives of benzene with more than one *ortho-para* directing substituent, derivatives with substituents in *meta* position to one another are more readily sulfonated than those in which the substituents are in *ortho* or *para* position.⁵ Among derivatives with *meta* directing substituents, those in which the substituents are in *meta* position to one another are sulfonated with difficulty.⁶

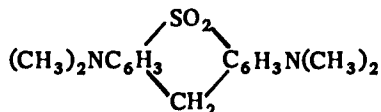
The sulfonation reaction is catalytically affected in a comparatively few cases.⁷ The most marked effect has been observed with mercury salts, which influence the position of attachment of the sulfonic group. Mercuric sulfate, for example, favors the formation of *para* disulfonic derivative on sulfonation of benzene sulfonic acid.⁸ Sulfonation of phthalic anhydride with sulfur trioxide in the presence of mercuric sulfate results in the formation of 3-sulfo- and 3,5-disulfophthalic anhydride, while in the absence of the catalyst, the 4-sulfonic derivative is obtained. Marked differences in orientation are observed in sulfonation reactions carried out with concentrated sulfuric and with fuming acid, in the presence of a *mercury salt*.⁹ Thus, in the presence of a little mercurous chloride, *nitrobenzene* and *benzoic acid* give 95% and 92% yield of the *meta* sulfonic derivative respectively with 92% sulfuric acid. On the other hand, sulfonation of nitrobenzene with fuming sulfuric acid of 20% sulfur trioxide content in the presence of mercury ions, gives 94% of the *ortho* isomer, and treatment of benzoic acid with fuming acid of 10% sulfur trioxide content in the presence of mercurous chloride gives 97% of the *ortho* sulfonic derivative.¹⁰ *Anthraquinone*, sulfonated with sulfuric acid alone, gives anthraquinone- β -sulfonic acid, while when treated with the same acid in the presence of 0.5% mercury, it is converted almost exclusively to the α -sulfonic compound.¹¹ Further sulfonation of anthraquinone-2-sulfonic acid in the presence of mercury salts results in the formation of 2,5- and 2,8-disulfonic acids, while sulfonation in the absence of mercury results in the formation of 1,6- and 1,7-disulfonic derivatives.

Boric acid has been employed as a catalyst in the sulfonation of β -naphthol.¹² This reagent causes an increase in the yield of the 1-sulfonic acid and 1,6-disulfonic derivative at the expense of the 6- and 8-sulfonic derivatives; it protects the hydroxy and amino groups in hydroxy and amino anthraquinones, facilitates sulfonation, and directs the sulfo group to definite positions. Boron

trifluoride is claimed to facilitate sulfonation and to exert a directive effect.⁵⁶⁶

Small amounts of *iodine* cause a sulfonation reaction to proceed at a lower temperature. Iodine is also believed to induce *para* sulfonation.¹³ Benzoic acid gives the meta sulfonic acid when sulfonated in the presence of iodine.

The presence of water may be detrimental in some cases; for example, in the preparation of tetramethyldiaminodiphenylmethanesulfonic acid, the sulfone



is formed if water is present in the sulfuric acid.

In many cases sulfuric acid acts as an oxidizing agent, and occasionally causes charring. The usual by-products of sulfonation with sulfuric acid or sulfur trioxide are sulfones.⁵⁸³ Sulfone formation may become the principal reaction at high temperatures.⁵⁸⁴ Benzidine gives benzidine sulfone as the main product with 40% oleum on one hour's heating at 100°. ⁵⁸⁵

Certain substituents may be modified during sulfonation. The methoxy group in 8-methoxyquinoline is demethylated by 83% sulfuric acid at 180°. The trifluoromethyl group in amino and nitrotrifluoromethylbenzenes is hydrolyzed to a carboxyl group during sulfonation.⁵⁸⁶ In the sulfonation of 4-chloro-2-nitro-4'-methylidiphenyl ether and of 4-methyl-2-nitro-4'-bromodiphenyl ether with concentrated sulfuric acid the halogen is replaced by the sulfonic group.⁵⁸⁷ Nitro and carboxylic groups may be replaced by the sulfonic group when sulfonation is effected under energetic conditions. In the sulfonation of compounds with phenolic hydroxyl groups with strong sulfuric acid, the sulfuric ester of the phenolic body may form. In such cases, the ester groups are destroyed by diluting the reaction product with water and heating.

Addition of sodium or ammonium sulfate prevents side reactions to a large extent in many cases, and may exert a directive influence.⁵⁸⁸

Sulfonation by Use of Sulfuric Acid^(*)

Aromatic compounds of sufficient reactivity may be readily sulfonated by means of concentrated sulfuric acid.

The usual *procedure* is to add the material to be sulfonated gradually to sulfuric acid of the proper concentration. Care may have to be exercised to prevent an unduly great rise in temperature during the addition of the aromatic body. If the substance to be sulfonated is insoluble in sulfuric acid, the mixture must be well agitated during the reaction.

After completion of the reaction, the mixture is poured on ice, or in water if acid of moderate strength has been employed as the sulfonating agent. Milk of lime or calcium carbonate is then added. If the sulfonic acid yields a soluble calcium salt, the solution

(*) Ordinary concentrated sulfuric acid of the present is 98% acid; concentrated acid of the early days did not exceed 95% strength. The so-called English acid was of 91% acid content. What is often termed *monohydrate* is a 100% acid.

is freed from the precipitated calcium sulfate by filtration and evaporated to a small volume; the liquid is again filtered and evaporated to crystallization. The calcium sulfonate may be salted out with sodium chloride in some cases; α - and β -naphthalene sulfonic acids have been isolated by this method.¹⁴ If the calcium salt of the sulfonic acids is insoluble in water the precipitate formed upon the addition of milk of lime or calcium carbonate is filtered, treated with dilute sulfuric acid, the free sulfonic acid is extracted with an organic solvent immiscible with water, and isolated by removal of the solvent.

The barium and lead salts of many aromatic sulfonic acids are soluble in water and may be isolated by adding an excess of the hydroxide or carbonate of these metals to the sulfonation mixture. The sulfuric acid is thereby neutralized and precipitated as the insoluble barium or lead salt, and is removed by filtration. The sulfonic acid may be freed from the solution of the lead salt by treatment with hydrogen sulfide, which removes the lead as the insoluble sulfide, and may be isolated from the filtered solution by removal of the water by distillation or evaporation. It should be noted that in the treatment of the sulfonic acid with lead hydroxide or carbonate, basic, insoluble lead sulfonates are apt to form, causing some loss of the sulfonated product.

Occasionally the acid sodium salt of disulfonic acids are only sparingly soluble in dilute sulfuric acid, and may be precipitated out by pouring the cooled sulfonation mixture into twice its volume of cold water and saturating the resulting solution with sodium chloride. The mono sodium salt of the sulfonic acid then separates on cooling and is filtered, washed with saturated sodium chloride solution, and is purified by crystallization from alcohol.¹⁵ Amino- β -naphtholdisulfonic acid has been isolated by this method.¹⁴

Another method of separation, applicable in special cases, is to add sufficient sodium chloride to the reaction mixture to convert the excess sulfuric acid into bisulfate, and to dilute the mixture with 10% of water, whereupon it separates into two layers, the upper consisting of the organic sulfonic acid.¹⁶

In some instances the sulfonic acid may be obtained directly in a crystalline state by cautiously diluting the sulfonation mixture with water.¹⁷ This procedure is often applicable to sulfonic acids derived from aromatic amines. Occasionally the sulfonic acid separates as a solid during sulfonation, as is the case with salicylic acid.¹⁸

Tests for Determining Completion of Sulfonation

A simple, and often satisfactory method for the determination of the end point of the sulfonation reaction is to mix a sample of the reaction mixture with water or dilute caustic; formation of a clear solution usually indicates that sulfonation is complete. In applying the test to amino compounds, dilute aqueous caustic should be used.

The course of sulfonation may be accurately followed by determining the acidity of the reaction mixture at intervals. When sulfonation is complete, there will be no further decrease in acidity.

A satisfactory method for the determination of the extent of sulfonation is as follows: A sample of the reaction mixture representing a known fraction of the total is diluted with water and is treated with an excess of barium carbonate; the solution is filtered and the precipitate is washed carefully free of the sulfonate. The combined filtrate and washings are made up to volume and an aliquot portion is titrated with standard potassium chromate solution, which precipitates the barium as barium chromate. The end point is determined by a spot test for potassium chromate with starch iodide paper. Carboxylic groups in the aromatic body react with barium carbonate in the same manner as the sulfonic group, and allowance must be made for this in the calculation if carboxylic groups are present in the aromatic sulfonic compound.

Sulfonation is carried out with sulfuric acid of various concentrations, de-

pending on the body to be sulfonated. Occasionally the use of 100% sulfuric acid, the so-called "monohydrate",¹⁹ is required.

Pure, 100% sulfuric acid is prepared as follows: Ordinary commercial concentrated sulfuric acid is mixed with sufficient fuming sulfuric acid to raise the concentration to 98%, and the liquid is cooled to at least 0° with agitation. Cooling and agitation are continued as long as crystals continue to form, and the crystals of the pure acid are finally freed from the mother liquid; they melt on warming to room temperature.

While sulfuric acid of 100% strength possesses a high degree of sulfonating power, this power may decrease rapidly with dilution. Thus, the velocity of sulfonation of *p*-nitrotoluene at 25° with 99.4% acid is about 1/800 of that with 100% acid.²⁰

A simple test is available for rapidly determining the approximate strength of a sample of concentrated sulfuric acid: Two to three cubic centimeters of the acid are mixed with a few decigrams of potassium perchlorate and the mixture is heated until fumes of perchloric acid are evolved. A 90–94% acid assumes a yellow color when treated in this manner; a 96–98% acid assumes a dark orange color, while 99–100% acid becomes brownish.

Sulfonation often proceeds effectively when ignited *infusorial earth* or finely subdivided *active carbon* is stirred into the reaction mixture to form a thick slurry that can still be agitated.²¹ Sulfonation may be effected also in an indifferent solvent, such as petroleum ether; the procedure is especially useful in sulfonating highly reactive compounds. In the *Black process*,²² the compound to be sulfonated is dissolved in glacial acetic acid, and the calculated amount of sulfuric acid is added. The sulfonated product is recovered by removing the acetic acid by distillation under vacuum. Arylamines have been sulfonated by adding molecular equivalents of the amine and sulfuric acid and a half molecular equivalent of sodium sulfate into decalin, heating the mixture to 190° in the course of 2 to 3 hours and maintaining this temperature for an additional 6 to 8 hours.

The sulfonating effect of sulfuric acid may be enhanced by the addition of phosphorus pentoxide.²³ The use of metaphosphoric acid in conjunction with sulfuric acid of 100% strength is also beneficial, and a mixture of 1 part of metaphosphoric acid and 1 part of sulfuric acid of this strength is shown to have the sulfonating power of fuming sulfuric acid of 20 to 25% sulfur trioxide content.²⁴

The Baking Process

Acid sulfates of aromatic amines undergo molecular rearrangement at 200–230° and form sulfonated amines:²⁵

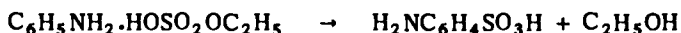


The sulfonic group enters the *para* position, unless this position is already occupied with a substituent. The reaction proceeds at somewhat lower temperature with certain aromatic amines. The method gives sulfonic acids not obtain-

able by direct sulfonation, or obtained only in small amounts. The optimum temperature for any particular amine sulfate should be determined by special tests for each individual case. It is desirable to carry out the "baking" under vacuum, in order to avoid any danger of carbonization, and to facilitate the transformation.²⁶ The yields of sulfonic acid obtained by the "baking" process are good, usually between 89 and 98%.

The acid sulfate is prepared by adding the amine to an equimolecular amount of 20% aqueous sulfuric acid, and evaporating the solution to dryness with stirring. The solid acid sulfate is removed, powdered and heated in shallow trays. In order to assure uniform heating, the salt must be spread out in a thin layer. The originally pasty mass generally turns to a solid upon completion of the reaction. The mass is cooled after this stage is reached, and is dissolved in dilute sodium hydroxide. The solution is filtered and boiled to expel the small amounts of unsulfonated base. The solution is finally concentrated to a point where sodium sulfate begins to crystallize and is acidified to free the sulfonic acid.

This transformation to a sulfonic acid takes place also with acid esters of sulfuric acid, with elimination of the alcohol:



The acid esters are formed by mixing the alcohol with concentrated sulfuric acid and allowing the mixture to stand for a time.

The procedure of sulfonation by use of sulfuric ester is as follows: Equal parts of sulfuric acid and alcohol are mixed, and after one hour, the mixture is diluted with water and saturated with calcium hydroxide. The solution is filtered and concentrated on the water bath and is mixed with an equivalent amount of the hot solution of the amine oxalate. The solution is again filtered and evaporated to dryness, and the solid residue is heated slowly to 200°. The resulting product is purified by crystallization from water.²⁷

Sulfonic acids are formed also by heating sulfamic acids, $\text{RNH} \cdot \text{SO}_3\text{H}$, alone or mixed with a half molecular equivalent of sulfuric acid.

Use of Bisulfates and Polysulfates

Certain aromatic bodies, especially those more readily sulfonated, such as phenols and amines, heated with an alkali metal bisulfate, are converted to sulfonates. Thus, *m*-cresol, mixed with four parts of freshly fused and powdered sodium bisulfate and heated to 100°, is converted to sodium *m*-cresolsulfonate. The reaction proceeds at different temperatures, depending on the character of the aromatic body. The results obtained by this method are seldom entirely satisfactory.

Better results are obtained by use of alkali metal *polysulfates*, which are molecular compounds of sulfuric acid with alkali metal bisulfates.²⁹ The yields of sulfonic acid are generally satisfactory when polysulfates are employed, and moreover, these reagents are free from the objectionable decomposing action of sulfuric acid. Monosodium disulfate, $\text{NaHSO}_4 \cdot \text{H}_2\text{SO}_4$, is a satisfactory sulfonating agent at high temperatures as well as at temperatures in the neighborhood of 100°, as it melts between 95° and 100°. This compound is prepared by

beating sodium bisulfate with an equivalent of sulfuric acid containing some water. The sulfonation reaction may be expressed as follows:



On neutralizing the reaction mixture, the sodium salt of the sulfonic acid is formed directly:



Sulfonation with Fuming Sulfuric Acid

Many aromatic bodies are destructively attacked by sulfuric acid at temperatures at which they may be appreciably sulfonated by this acid. Such substances are often satisfactorily sulfonated with fuming sulfuric acid.³⁰ The difference in the sulfonating power of fuming sulfuric acid and of concentrated acid may be appreciated from the fact that sulfonation of *p*-nitrotoluene at ordinary temperature with oleum of 2.4% sulfur trioxide content proceeds almost six thousand times as rapidly as with acid of 99.4% strength.²⁰ Acid containing varying amounts of free sulfur trioxide is used, depending on the substance to be sulfonated, and the degree of sulfonation desired.

Sulfonation with fuming sulfuric acid may be carried out by adding the substances to be sulfonated to the required amount of oleum of the appropriate strength. Where the reaction proceeds too violently if carried out directly in the fuming acid, an excellent method is to dissolve the substance to be sulfonated in acid of 100% strength, and to introduce the required amount of oleum gradually with good agitation. The vigor of the reaction may be abated in some cases by adding sand to the reaction mixture.

Gaseous sulfuric anhydride has been employed for the purpose of sulfonation.³¹ The anhydride may be prepared readily by heating fuming sulfuric acid of the highest anhydride content and condensing the vapors which are given off. Sulfur trioxide has been employed in the form of its addition compound with weakly basic substances, such as dioxane or pyridine.

Sulfonation with Sulfur Trioxide^(*) and its Addition Compounds

Sulfonation of liquid hydrocarbons with sulfur trioxide may be carried out by conducting a current of gaseous sulfur trioxide into the hydrocarbon maintained at the proper temperature.⁵⁸⁹

Sulfur trioxide may be employed in solution in sulfur dioxide,⁵⁹⁰ or in chlorinated aliphatic hydrocarbons, such as chloroform.

Sulfonation in solution in chloroform may be carried out in the following manner: The compound to be sulfonated is dissolved in three to five times its weight of chloroform, the solution is cooled to 0° in ice or ice-salt mixture and the calculated quantity of sulfur trioxide is introduced, generally in the gaseous form with a current of nitrogen.

(*)The γ -modification alone among the three modifications of sulfur trioxide are employed for purposes of sulfonation. The compound is generally stabilized with boric anhydride or phosphorus pentoxide.

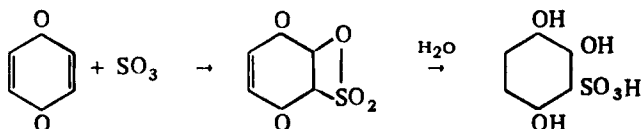
The mixture is maintained at 0° for one hour, and at room temperature for two hours with good agitation; it is then poured on ice, the chloroform layer holding the sulfonic acid in solution is separated and the sulfonic acid is isolated by the appropriate procedure.⁵⁹¹

Sulfur trioxide occasionally causes oxidative side reactions. This tendency is overcome by using addition compounds of sulfur trioxide. Among the latter, the mildest sulfonating agents are addition compounds of sulfur trioxide with dioxane, and pyridine or other tertiary bases, and these are the agents generally employed.⁵⁹²

The *sulfur trioxide-dioxane adduct* is made by adding 80 gm of sulfur trioxide to a solution of 88 gm pure dioxane in 300 cc ethylene chloride cooled to 0°. The adduct separates in the form of a colorless crystalline solid which is filtered and dried in a desiccator.⁵⁹³

The *sulfur dioxide-pyridine adduct* is prepared by adding a solution of 62 gm anhydrous pyridine in 350 cc chloroform cooled to 0° drop by drop to 38.5 gm chlorosulfonic acid. The adduct separates as a precipitate; it is filtered, washed rapidly with 30 to 40 cc portions of cold chloroform four times, dried first on a porous plate then in a desiccator. The adduct is obtained in a 62% yield.⁵⁹⁴ The adduct may also be prepared simply by adding sulfur trioxide cautiously and with stirring to a solution of pyridine in chloroform cooled with ice-salt mixture. The precipitated adduct is filtered, washed with chloroform, and is dried in vacuum.⁵⁹⁵

Cyclopentadiene has been successfully sulfonated to $\Delta^{2,3,4,5}$ -cyclopentadienesulfonic acid by heating at 50 to 80° four hours with the sulfur trioxide-pyridine adduct under a nitrogen atmosphere.⁵⁹⁶ Heterocyclic compounds may be sulfonated in high yields without resinification by heating at 60 to 140° in a sealed tube with the pyridine adduct.⁵⁹⁷ *p*-Benzoquinone is converted to hydroxyhydroquinone sulfonic acid by sulfur trioxide:⁵⁹⁸



The sulfur trioxide-pyridine adduct reacts with a molecular equivalent of sulfur trioxide to form a crystalline pyridine-bis-(sulfur trioxide) complex. The complex converts thiophene to thiophene-2-sulfonic acid in 86% yield, while the simple pyridine-sulfur trioxide adduct yields a mixture of thiophene mono- and -disulfonic acids. 2,5-Dimethylthiophene gives the 3-sulfonic acid with the bis-adduct.

In sulfonation reactions with sulfur trioxide no water is formed and sulfonation occurs only at restricted positions; for example, only at the meta or para positions. Naphthalene gives only the α -sulfonic acid when treated with sulfur trioxide at 140°. Sulfonation with sulfur trioxide generally follows the Armstrong and Wynne rule.

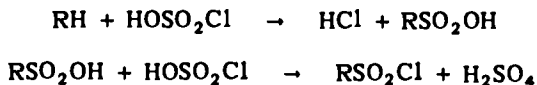
In reactions with sulfur trioxide, there is a tendency toward the formation of sulfones in addition to sulfonic acids. Sulfone formation may be reduced to a minimum, or completely eliminated by the addition of a dehydrating agent.

Sulfonation with Pyrosulfuric Acid

Sulfonation of aromatic bodies may be effected with pyrosulfuric acid, $(\text{HO})_2\text{SO}_2\text{SO}_3$, or its dipotassium salt. The latter may be prepared by heating potassium hydrogen sulfate at 270 to 330°, reaction being complete as soon as a rapid rise in temperature sets in. Pyrosulfuric acid is a vigorous oxidizing agent, and sulfonation reactions with it should be carried out with care. Phloroglucinol and pyrogallol are very readily sulfonated at 2- and 4-position with pyrosulfuric acid.⁵⁹⁹ Chloronaphthalenedisulfonic acids may be prepared from the monosulfonic acids by the action of pyrosulfuric acid at 100°. ⁶⁰⁰

Sulfonation by Use of Chlorosulfonic Acid

The direct sulfonation of aromatic bodies with sulfuric acid or oleum at times presents difficulties because of the insufficient reactivity of ordinary sulfuric acid on the one hand, and the extremely energetic action of fuming sulfuric acid on the other. In such cases, good results are often obtained by use of chlorosulfonic acid, HOSO_2Cl , also termed sulfonyl oxychloride. The use of chlorosulfonic acid offers the further advantage that the reaction proceeds without the formation of by-products. The reaction first results in the formation of the sulfonic acid, but an excess of the reagent converts this to the sulfonyl chloride:³²



Sulfonation with chlorosulfonic acid proceeds under mild conditions, and substituents that are sensitive to sulfuric acid may remain unaffected. Sulfonation with chlorosulfonic acid may cause the entrance of the sulfonic groups in positions other than those observed with sulfuric acid.⁵⁶⁷

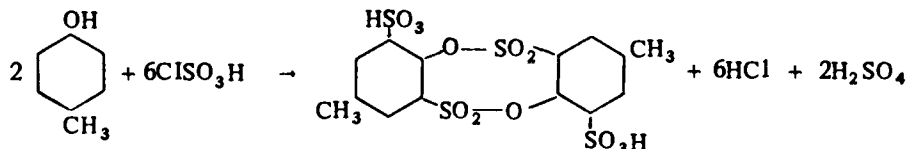
The usual procedure is to dissolve or suspend the compound to be sulfonated in an inert solvent, such as tetrachloroethane, carbon disulfide, nitrobenzene, etc., and to add the required amount of chlorosulfonic acid gradually with stirring. The reaction is completed by heating, if necessary. The end of the reaction is indicated by the fact that hydrochloric acid is no longer evolved from the reaction mixture. The product may be recovered as the alkali metal sulfonate.

Hydrolysis of sulfonyl chlorides to sulfonic acids may be brought about by boiling with alcohol, aqueous alcohol, acetic acid, or formic acid. Hydrolysis with the last mentioned is a particularly effective method.⁵⁶⁹

The sulfonyl chloride is readily obtained by reacting the aromatic body with a large excess of chlorosulfonic acid, usually five times the theoretically required amount. After the completion of the reaction, the mixture is poured onto ice, whereupon the aromatic sulfonyl chloride separates from the aqueous acid as an oily layer.

Side reactions may occur in the sulfonation with chlorosulfonic acid. The latter may cause oxidation or chlorination, especially under drastic conditions.⁶⁰¹ The Jacobson rearrangement may also take place under the influence of chlorosulfonic acid. Carboxylic groups, if present in the aromatic compound,

are converted to carboxylic chloride groups by the action of chlorosulfonic acid, and amino groups are converted to sulfoamino groups, unless they have been acylated before the compound is subjected to the action of the reagent. Phenolic hydroxyl groups are replaced with chlorine on energetic treatment with chlorosulfonic acid. Phenols may be sulfonated, however, by treatment with chlorosulfonic acid at a moderate temperature, although if the reaction is carried out at a low temperature the principal product obtained is a phenyl hydrogen sulfate.³³ The reaction is useful for the preparation of *ortho*-sulfonated amines which are otherwise difficultly accessible. A number of substituted phenols are converted on energetic treatment with chlorosulfonic acid into sulfonilides, bimolecular compounds containing two sulfonic ester groups:



The temperature at which the reaction is carried out varies, depending on the character of the compound to be sulfonated. Benzoic acid is converted to the *m*-chlorosulfonyl derivative at 125°; acetanilide gives the *para*-sulfonated derivative at 60°; salicylic acid is sulfonated at 75°, while the reaction with *p*-tolyl methyl ether proceeds at 0°.

Chlorosulfonic acid is obtained in nearly theoretical yield by conducting gaseous hydrogen chloride into well cooled fuming sulfuric acid of 40% SO₃ content until the liquid is fully saturated with the gas. The chlorosulfonic acid is isolated and purified by fractional distillation (b.p. 149–151°).³⁴ The compound may also be prepared conveniently by adding common salt to fuming sulfuric acid diluted with concentrated sulfuric acid.

Chlorosulfonic anhydride, S₂O₅Cl₂, (pyrosulfuryl chloride), sodium chloropyrosulfonate, and *fluorosulfonic acid* have also been employed as sulfonating agents. Chlorosulfonic anhydride acts both as a sulfonating and chlorinating agent.⁶⁰² Sulfonation takes place when the reaction is carried out at –23° in carbon tetrachloride solution.⁶⁰³ In sulfonation reactions with sodium chloropyrosulfonate, the point of entrance of the sulfonic group may be influenced by the solvent; in ethyl acetate, 2-hydroxycarbazole-3-sulfonic acid is obtained from 2-hydroxycarbazole, while in acetic acid 2-hydroxycarbazole-7-sulfonic acid is formed.⁶⁰⁴

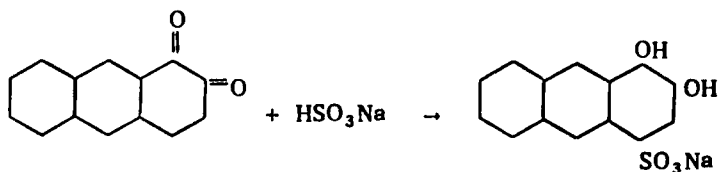
Fluorosulfonic acid is a less vigorous sulfonating agent than chlorosulfonic acid, and the reaction with this reagent should be carried out at a higher temperature and, if necessary, under pressure. In general, however, the reaction proceeds well at room temperature. Fluorosulfonic acid shows practically no oxidative reactions.⁶⁰⁶ Carbon tetrachloride may be employed as a solvent in the reaction, but chloroform and *n*-pentane are attacked by the reagent at room temperature.

Thionyl chloride, SOCl₂, which usually acts as a chlorinating agent, can

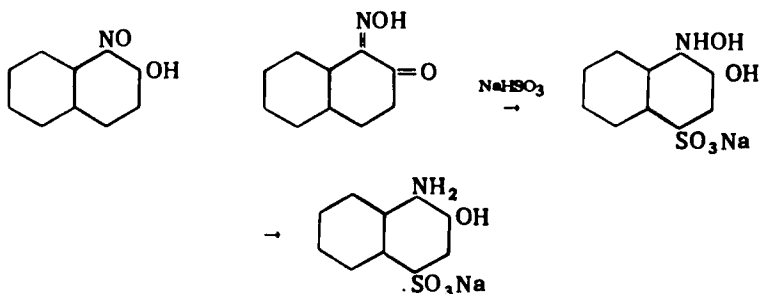
also act under some circumstances as a sulfonating agent;³⁵ when acting in the latter capacity, the compound behaves as though it consisted of a mixture of sulfur chloride, SCl_2 , and sulfuryl chloride, SO_2Cl_2 .

Sulfonation by Use of Sulfites

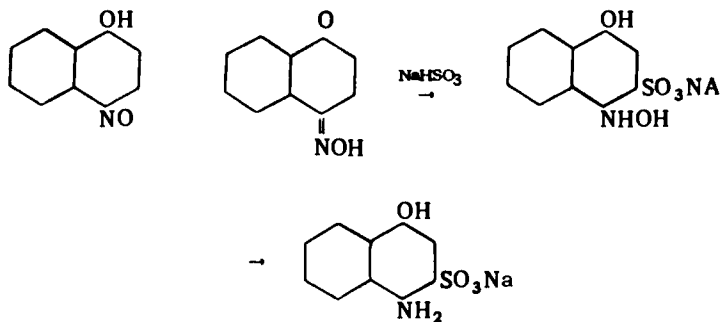
Certain organic bodies susceptible to reduction, give sulfonates upon treatment with alkali metal bisulfites. Thus, 1,2-anthraquinone, subjected to the action of sodium bisulfite, is converted to sodium 1,2-dihydroxyanthraquinone-4-sulfonate:³⁶



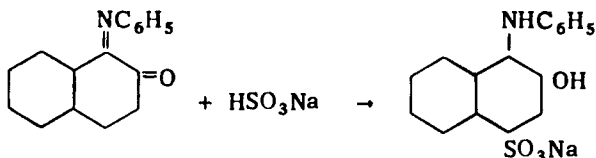
The compound may be converted to sodium 1,2-anthraquinone-4-sulfonate by oxidation with chromic acid. 1-Nitroso-2-naphthol, which also exists in the tautomeric o-naphthoquinonemonoxime form, gives a hydroxamic sulfonate, which is further reduced to sodium 1-amino-2-hydroxynaphthalene-4-sulfonate:³⁷



The reaction with 4-nitroso-1-naphthol proceeds similarly:



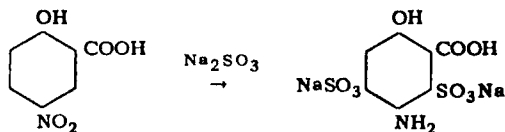
1-Phenylimino-2-naphthoquinone is converted in a similar manner to sodium 1-phenylamino-2-hydroxy-4-sulfonate:³⁸



Resorcinol, α -naphthol, hydroxynaphthoic acids, etc. have been sulfonated by sodium sulfite in the presence of oxidizing agents.⁶⁰⁶ Aromatic amines, including aniline, α -naphthylamine, *p*-phenylenediamine, diethyl-*p*-phenylenediamine have also been sulfonated by sulfites in the presence of oxidizing agents.⁶⁰⁷

Many nitro compounds, subjected to the action of sodium bisulfite, are partially reduced and simultaneously sulfonated (*Piria reaction*). Reaction may be brought about by refluxing a mixture of the nitro compound and the bisulfite.³⁹ A sulfoarylsulfonic acid is formed simultaneously with the arylaminosulfonic acid. The ratio of the amounts of these two types of compounds formed in any particular instance depends upon the substituents present in the original aromatic body, and to some extent also upon the alkalinity of the sulfite solution.⁴⁰ The reaction is applicable to *m*-dinitrobenzene and its homologs.⁴¹ α -Nitronaphthalene gives an 80% yield of 1-naphthylamine-2,4-disulfonic acid with sodium bisulfite.⁴² Both nitro groups in 1,8-dinitronaphthalene are reduced to amino groups, and three sulfonic groups enter the nucleus.⁴³ Acylated dinitro-diaminoanthraquinone, boiled under reflux with four to five parts of sodium bisulfite, gives tetraminoanthraquinonesulfonic acids.⁴⁴

A vigorous reaction ensues when sodium sulfite is added to a concentrated hot solution of the salt of an aromatic nitro carboxylic acid; the nitro group is reduced to an amino group, and mono and disulfonic compounds are formed. The reaction proceeds even in an alkaline solution, and disulfonates are obtained even when a molecular equivalent of the bisulfite is employed. The disulfonic bodies are obtained in greater amount when the solution is made alkaline initially. Heating 5-nitrosalicylic acid with a large excess of sodium bisulfite results in the formation of a disulfonic acid.⁴⁵



Many azo dyes are capable of reacting with bisulfite to form sulfonic acids.⁴⁶

Sulfurous acid, reacting with phenolic bodies or aromatic amines in the presence of formaldehyde, gives methylsulfonic compounds, i.e., substances containing the grouping $\text{CH}_2\text{SO}_3\text{H}$. Aromatic bodies of the anthracene series also yield methylsulfonic derivatives under these conditions. Aminoanthraquinones give methylsulfonic derivatives with the methylsulfonic group attached to the nitrogen of the amino group.⁴⁷

Preparation of Sulfonic Acids by Oxidation of Thiols and Sulfinic Acids

Aromatic thiophenols may be converted to sulfonic acids by oxidation with various agents; the most commonly used of these is alkaline potassium permanganate.⁴⁸ Nitric acid has also been used for the purpose.⁴⁹ Many di- and trisulfonic acids of the naphthalene series have been prepared by this method.⁵⁰ *p*-Thiocresol in the form of its orthocarbonic ester has been oxidized at 0° in chloroform solution to the corresponding sulfonic acid with perbenzoic acid.⁵⁷⁰ In many cases oxidation must be effected under energetic conditions. In the preparation of naphthalene-1-2-disulfonic acid, for example, a large excess of permanganate must be used; in the preparation of 2,3,6-naphthalenetrisulfonic acid, from naphthalene-3,6-disulfonic acid 2-thiol, double the required quantity of permanganate should be used at 40 to 50°. The thiols required for the reaction are often readily obtained from the corresponding diazo compound and xanthates by the Leuckart reaction. Thiols may be oxidized with chlorine or bromine, but the compounds that result are the halides of the sulfonic acids.⁵¹ A number of aromatic disulfides have been oxidized by chlorine to the corresponding sulfonyl chlorides, among these are bis-(2-nitro-4-methylphenyl)- and bis-(3-bromo-4-methylphenyl)sulfides.⁵²

Sulfinic acids are also readily converted to sulfonic acids by treatment with suitable oxidizing agents. Potassium permanganate may be used satisfactorily for the purpose.

The usual procedure is to add a solution of potassium permanganate in excess to one of the sulfinic acid, and to warm the mixture for a short period. The excess of permanganate is destroyed by adding a little alcohol, the liquid is filtered and evaporated to dryness.⁵³

This method is of preparative value, since sulfinic acids are obtainable from aromatic diazo compounds by reaction with sulfurous acid in the presence of copper, and they may also be prepared by the Friedel-Crafts and Grignard reactions. Sulfonates have been prepared by this method from 3,5- and 2,3-dimethylbenzenesulfinic acids, 2- and 4-methoxybenzenesulfinic acid, and tetralin-1-sulfinic acid.⁵⁴

Aromatic sulfonyl halides have been obtained by treatment of sulfinic acids or their sodium salts in aqueous solution with chlorine or bromine.⁵⁵

Preparation of Sulfonic Acids by Replacement of Halogens and Nitro Groups

A halogen atom attached to an aromatic nucleus, if sufficiently activated, may be replaced with a sulfonic group by reaction with an alkali sulfite. With the less reactive bodies it may be necessary to heat the aromatic compound with an aqueous solution of the sulfite in an autoclave at 180-200° in the presence of a little copper sulfate.⁵⁶ An equimolecular quantity of a 15% solution of the sulfite is generally used.

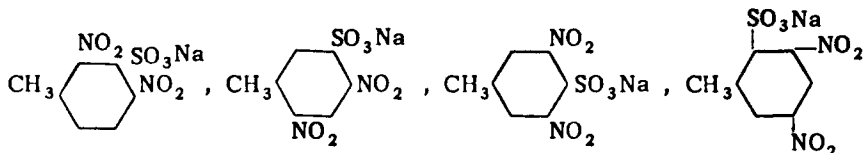
A bromine atom in the *para* position to an acylated amino group is thus replaceable with a sulfonic group. Benzaldehyde-*o*-sulfonic acid may be obtained from *o*-chlorobenzaldehyde by heating this compound with about two molecular equivalents of sodium sulfite solution in an autoclave at 170-180° for eight hours.⁵⁷ Benzaldehyde-*o,p*-disulfonic acid has been obtained similarly from *o,p*-dichlorobenzaldehyde by heating with aqueous sodium bisulfite in an autoclave at 190-200° for nine to ten hours.⁵⁸ *o,m*-Dichlorobenzaldehyde gives chlorobenzaldehydesulfonic acid under the same conditions.⁵⁹ 4-Chlorobenzoic acid, heated in an autoclave at 170° for sixteen hours with an excess of 20% aqueous sodium sulfite, is converted to sodium-4'-sulfo-2-benzoylbenzoate, which is readily cyclized to anthraquinone-2-sulfonic acid by heating with sulfuric acid.⁵⁹ This compound serves for the technical preparation of 2-aminoanthraquinone. 3-Chloro-2-naphthol, heated with aqueous sodium sulfite, gives 2-naphthol-4-sulfonic acid; 1,3-dichloro-2-naphthol gives 2-naphthol-3-sulfonic acid.⁶⁰

When the halogen is in an *ortho* or *para* position to a nitro group, the reaction proceeds readily on heating the compound with the sulfite solution under reflux. In some instances the reaction even takes place in the cold. Trinitrobenzenesulfonic acid has been obtained by heating an alcoholic solution of picryl chloride on a water bath for a short time with solid sodium bisulfite.⁶¹

2-Chloro-5-nitrobenzaldehyde reacts readily when boiled with aqueous sodium sulfite to form 2-sulfo-5-nitrobenzaldehyde.⁶² The bromine in bromoanthragallol is quite reactive, and a sulfonic acid may be obtained from this compound by heating it to boiling for a short time with 40° Bé bisulfite solution.⁶³ Bromanil, $C_6Br_4O_2$, treated with a concentrated solution of potassium sulfite, gives the potassium salt of thiochronic acid, $HO\cdot C_6H(SO_3K)(SO_3K)_4 \cdot 4KCl$, as the principal product; on the other hand, reaction with dilute solutions of bisulfite leads to the formation of dibromohydroquinone-disulfonic acid.⁶⁴

A nitro group attached to an aromatic molecule is replaceable, in certain compounds, with a sulfonic group; this is the case especially with some polynitro compounds.

One of the nitro groups in the four unsymmetrical trinitrotoluenes, for example, is easily replaceable by a sulfonic group on treating the nitro compound in the cold with a saturated solution of sodium sulfite. The dinitrosulfonic acids obtained from the various isomeric trinitrotoluenes were the following:⁶⁵



The 3-nitro group in 3,4-dinitrochlorobenzene is replaced with a sulfonic group when heated for several days with aqueous sodium sulfite.⁶⁶ 9-Nitroanthracene reacts readily, when heated with aqueous sodium sulfite, to give the corresponding sulfonic acid with replacement of the nitro group.⁶⁷ 1-Nitro- and 1,5- and 1,8-dinitroanthraquinone react when heated with aqueous sodium bisulfite in the presence of copper, with replacement of the nitro groups.⁶⁸ In some cases replacement of a nitro group also involves a migration of the entering sulfo group.^{56b}

Replacement of the Diazonium Group with the Sulfonic Group

A few sulfonic acids have been prepared directly from diazonium salts by replacement of the diazo group with a sulfonic group.⁶⁹ Thus, benzenediazonium sulfate is transformed to benzenesulfonic acid by treatment with a sulfite in the presence of cuprous hydroxide; the three toluene diazonium chlorides have been converted to the corresponding sulfonic acids by reaction with sulfurous acid.

Sulfonation of Various Types of Compounds

Sulfonation of Aromatic Hydrocarbons

Aromatic hydrocarbons are sulfonated with comparative ease; homologs of benzene are sulfonated with greater ease than benzene itself. Naphthalene and anthracene are very readily sulfonated, while highly methylated derivatives of benzene are sulfonated more readily than either naphthalene or anthracene.

Benzene can be sulfonated with concentrated sulfuric acid by heating a mixture of the hydrocarbon with the acid at a sufficiently high temperature.⁷⁰ The hydrocarbon may be monosulfonated by running it into one quarter its weight of 100% sulfuric acid and heating the mixture at 80° under reflux, until the whole of the benzene passes into solution. The sulfonic acid is obtained by this method in almost quantitative yield.⁷¹ Sulfonation proceeds nearly to completion when benzene and sulfuric acid of 66° Be are mixed with sufficient ignited infusorial earth to form a thick slurry still capable of being agitated, and the mixture is heated. Sulfonation of benzene has also been effected by passing vapors of benzene for a prolonged period into concentrated sulfuric acid heated at 100°. The vapors of benzene remove the water gradually from the hot acid, concentrating the latter to the point where reaction proceeds at a satisfactory rate.⁷² Homologs of benzene may also be sulfonated by this method.

Benzene may be monosulfonated readily at ordinary temperature with sulfuric acid containing 5 to 9.5% of sulfur trioxide, without the formation of any appreciable quantity of disulfonic acids.⁷³

Benzene, heated with twice its volume of 20% oleum, gives benzene *m*-disulfonic acid.⁷⁴ A mixture of isomeric benzenedisulfonic acids is formed when the hydrocarbon is heated at 250° in an autoclave with 150% excess of 95% sulfuric acid containing 0.1% of sodium sulfate.⁷⁵ It is claimed that the proportion of the *para* isomer increases if the reaction is carried out in the presence of a little mercury or ferrous sulfate.⁷⁶ The disulfonic acids are obtained in 90% yield when benzenesulfonic acid or its sodium salt is heated to 220-260° with 300% excess of sulfuric acid. When benzenesulfonic acid or its sodium salt is heated at 200° with one and a half times its weight of sodium trihydrogen disulfate, $\text{NaH}_3(\text{SO}_4)_2$, for two to three hours, benzene-*m*-disulfonic acid is obtained as the principal product, together with a small amount of the *para* disulfonic acid.

Benzene-1,3,5-trisulfonic acid has been obtained by heating potassium benzene-*m*-disulfonate with concentrated sulfuric acid on a free flame.⁷⁷ The compound has been prepared also by heating benzene-*m*-disulfonic acid, or preferably its potassium salt, with 50% excess of an alkali metal trihydrogen disulfate at 280-300° until charring just

begins. The compound has been prepared directly from benzene by heating the hydrocarbons at 280-290° with a mixture of sulfuric acid and phosphorus pentoxide.⁷⁸ A satisfactory method consists in heating benzene-*m*-disulfonic acid at 225° with oleum in the presence of mercury.⁷⁹

Benzene added to an excess of chlorosulfonic acid at room temperature gives *benzene* sulfonyl chloride in 70% yield.⁸⁰ *m*-Benzenedisulfonyl chloride is formed, together with a small amount of the *p*-isomer, on dissolving benzene in 10 parts of chlorosulfonic acid, and heating the mixture at 150-160° for 2 hours.⁸¹

Toluene sulfonates more readily than benzene; it is attacked by sulfuric acid of 96 to 100% strength readily at 35°, and slowly at 0°. ⁸² *Para*-toluenesulfonic acid is the principal product of the reaction at higher temperatures; at 75° the *para* isomer forms 75% of the total sulfonates, the *ortho* and *meta* isomers forming 19% and 6% of the total, respectively. The results obtained with oleum differ little from those obtained with concentrated sulfuric acid.⁸³ The *p*-isomer may be separated from the other isomers by making use of its lower solubility in water.¹⁷

The quantitative sulfonation of toluene in "petroleum toluene" has been effected satisfactorily with 3% oleum.⁸⁴

Sulfonation of toluene with oleum at high temperatures results in the formation, principally, of *toluene*-2,4-disulfonic acid, together with a little of the 2,5-isomer.⁸⁵ *Toluenetrisulfonic* acid has been prepared through the reaction of potassium toluenedisulfonate with chlorosulfonic acid at 240°. ⁸⁶ Sulfonation of potassium toluene-2,4-disulfonate with three molecular equivalents of chlorosulfonic acid at 240° gives the 2,4,6-trisulfonic derivative.⁸⁶

The reaction of chlorosulfonic acid with toluene at 75° to 80° results in the formation of *p*-toluenesulfonyl chloride in 95% yield, together with a little of the *ortho* isomer. The *ortho* isomer forms in greater proportion at lower temperatures.⁸⁷

Ortho and *meta* xylenes are readily sulfonated in the cold, the *meta* compound more readily than the *ortho* isomer.⁸⁸ *o*-Xylene is converted to the 4-sulfonic acid by warming with an equal volume of sulfuric acid.⁸⁹ *m*-Xylene also yields the 4-sulfonic acid as the principal product.⁹⁰ *p*-Xylene is more difficult to sulfonate than either *ortho* or *meta* xylene.⁹¹ *p*-Xylene-2,6-disulfonic acid is formed as the principal product on heating *p*-xylene at 140°-150° with 20% fuming sulfuric acid.⁹² Reaction of the hydrocarbon with chlorosulfonic acid results in the formation, principally, of the 2,6-disulfonyl chloride, with smaller amounts of the 2,5-isomer and of *p*-xylyl sulfone.⁹³

1,2,3-Trimethylbenzene (hemimellitene) reacts readily with sulfuric acid to form the 4-sulfonic acid.⁹⁴ *2,2,4-Trimethylbenzene* (pseudocumene) also reacts readily giving the 5-sulfonic acid.⁹⁵ The reaction proceeds with ease also with *1,3,5-trimethylbenzene* (mesitylene).⁹⁶ Sulfonation of tetramethylbenzenes is complicated by the fact that molecular rearrangements often occur during the reaction (Jacobsen's reaction).⁹⁷ *1,2,3,4-Tetramethylbenzene* (prehnitene) is sulfonated readily with no molecular rearrangement.⁹⁸ *1,2,4,5-Tetramethylbenzene* (durene) treated with sulfuric acid gives a mixture of two isomeric trimethylbenzenesulfonic acids and pentamethylbenzene.⁹⁹ *Pentamethylbenzene*, subjected to the action of sulfuric acid, gives 1,2,3,4-tetramethylbenzenesulfonic acid.

n-Propylbenzene, treated with sulfuric acid or oleum, gives largely the *p*-sulfonic acid, with a little of the *ortho* isomer. *Isopropyl*- and *n*-butylbenzene behave in a similar manner.¹⁰⁰ *p*-Isopropyltoluene (cymene), sulfonated at 0° with oleum, yields largely the 2-sulfonic acid.¹⁰¹ Benzene homologs with long chain substituents are sulfonated predominantly at the *p*-position.

Biphenyl and its derivatives, subjected to the action of sulfonating agents, tend to form 2,2'-cyclic sulfones. *4-Biphenylsulfonic acid* results when biphenyl is heated with an equal amount of sulfuric acid.¹⁰² The compound is obtained in better yield on heating biphenyl in solution in nitrobenzene with sulfuric acid.¹⁰³ *Biphenyl-4,4'-disulfonic acid* results in almost quantitative yield by heating biphenyl with an excess of sulfuric acid.¹⁰⁴ The compound may be isolated as the slightly soluble potassium salt by precipitation with 20% potassium chloride.

Phenylcymene has been monosulfonated by treatment with cold fuming sulfuric acid containing 3% sulfur trioxide.¹⁰⁵

Diphenylmethane in chloroform solution, treated with chlorosulfonic acid, is converted to the 4-sulfonic acid, while treatment at 100° with oleum results in the formation of the 4,4'-disulfonic acid.¹⁰⁶

Naphthalene is readily sulfonated with concentrated sulfuric acid even in the cold.¹⁰⁷ The sulfonic group enters the α -position when the sulfonation is carried out at a low or moderate temperature, but at higher temperatures greater proportions of the β -acid are formed. The percentage of the α -sulfonic acid on the basis of the total sulfonic acid formed at 40°, 100°, 124°, and 150° are 96.0%, 83.0%, 52.4%, and 18.3% respectively, the remainder of the sulfonated product consisting largely of the β -isomer.¹⁰⁸ It may be pointed out that naphthalene- α -sulfonic acid is hydrolyzed more readily than the β -acid. This fact probably plays an important role in the transformation of the α -acid to the β -isomer. Naphthalene in the solid state may be employed successfully for the preparation of the sulfonated derivatives of this hydrocarbon, providing the reaction mixture is effectively agitated.

A satisfactory method for the preparation of *naphthalene- α -sulfonic acid* is to add naphthalene in very finely divided condition with good agitation to about twice its weight of 100% sulfuric acid maintained at 0°. Agitation is continued at this temperature for an hour, after which the mixture is poured into water.¹⁰⁹ α -Sulfonation may also be effected with 25-40% excess of 93 to 98% sulfuric acid. Completion of the sulfonation may be ascertained by subjecting a portion of the reaction mixture to steam distillation; no naphthalene distills over if the reaction has come to an end.

Naphthalene- β -sulfonic acid may be prepared as follows: One part of finely ground naphthalene and 1.6 parts of 94% sulfuric acid are mixed and heated at 160° for five minutes, and then poured into 1.2 parts of water. On cooling the resulting solution, the greater proportion of the β -sulfonic acid crystallizes out as the trihydrate, together with a small quantity of the 2,2'-sulfone.¹¹⁰

Both naphthalene- α -sulfonic acid and the β -isomer may be purified by crystallization from hydrochloric acid.

In the sulfonation of naphthalene to the 2-sulfonic acid on the commercial scale, the use of excess of sulfuric acid may be avoided by heating the hydrocarbon with the theoretically required amount of 93% sulfuric acid at 155°, under an absolute pressure of 600 mm.¹¹¹ The 2-sulfonic acid is usually converted to its sodium salt. This may be accomplished by adding the calculated quantity of sodium sulfate to the reaction mixture, then neutralizing the acid with lime or calcium carbonate; the sodium sulfonate remains in solution, and is freed from the precipitated calcium sulfate by filtration. Alternatively, the sulfonic acid is converted to the soluble calcium salt by the addition of lime or calcium carbonate, and the filtered solution is boiled with the calculated

amount of sodium carbonate. This causes the precipitation of the calcium as the carbonate, and converts the sulfonic acid to its sodium salt, which remains in solution. The calcium salt of the β -acid is less soluble than that of the α -acid; consequently it is possible to bring about a partial separation of these acids on conversion to their calcium salts.

Naphthalene may be *disulfonated* at higher temperatures by use of oleum.¹¹² The limiting π values for the disulfonation of naphthalene, i.e., the limiting concentration of the acid expressed as total percent SO_3 , at which disulfonation takes place are 82 at 10° , 80 at $80\text{--}90^\circ$, and 66.5 at 160° .

In the sulfonation of naphthalene, the sulfo group can never enter the *para* and *peri* position to each other (*Armstrong and Wynne rule*). In hydroxy and aminonaphthalenes, however, the sulfonic group can occupy *ortho* and *para* positions.^{125, 608}

Treatment of one part of naphthalene with five parts of oleum of a little over 30% sulfur trioxide content at 40° results in the formation of 70% of *naphthalene-1,5-disulfonic acid* and 25% of the 1,6-isomer. When the sulfonation is carried out at 130° with oleum of the same strength, the product consists chiefly of the 1,6- and 2,7-disulfonic acids.¹¹³ On effecting the sulfonation at 165° , the chief product is the 2,7-acid, with minor proportion of the 2,6- and 1,6-acids. The separation of the 1,5-naphthalenedisulfonic acid from a mixture of the 1,5- and 1,6-acids may be brought about by adding sodium chloride to their solution, which precipitates out the 1,5-naphthalenedisulfonic acid as its sodium salt.

The sulfonation of naphthalene-1-sulfonic acid with oleum at 40° results in the formation of the 1-5-disulfonic acid. On further sulfonation in the cold, naphthalene-2-sulfonic acid gives the 1,6-acid in 80% yield, together with 20% of the 1,7-disulfonic acid.¹¹⁴ Sulfonation at 100° gives the 1,6-isomer as the principal product; at 160° some of the 2,7-isomer also forms, while at 180° , the 2,6-isomer is formed in not more than 30% yield.¹¹⁵ A continuous process for the preparation of the 2,7-disulfonic acid in 78-85% yield has been developed, making use of the vapor-phase sulfonation of naphthalene at $220\text{--}245^\circ$ with 80-95% sulfuric acid.¹¹⁶

The quantitative estimation of the various acids in a mixture may be carried out by taking advantage of the differences in solubilities of the calcium, barium, and lead salts of the acids.¹¹⁷

Sulfonation of naphthalene with 20% oleum, followed by heating the reaction mixture at 250° for 10 hours with a large volume of concentrated sulfuric acid, results in the formation of disulfophthalic acid. Monosulfophthalic acid is obtained if the reaction temperature is held at 220° .

Naphthalene may be sulfonated to the 1,3,6-trisulfonic acid by adding 1 part of the hydrocarbon to 8 parts of fuming sulfuric acid containing 24% of sulfur trioxide and heating the mixture at 180° for a few hours.¹¹⁸ Trisulfonation may be effected successfully at water bath temperature by use of oleum of 40% SO_3 content.¹¹⁹

Naphthalene-1,3,5-trisulfonic acid is formed on dissolving naphthalene-1,5-disulfonic acid in 100% sulfuric acid, adding 67% oleum, and warming to 90° .¹²⁰ Naphthalene-2,6-disulfonic acid, sulfonated at 100° with oleum, gives *naphthalene-1,3,7-trisulfonic acid*.¹²¹

Naphthalene has been tetrasulfonated by heating at 260° with a mixture of sulfuric acid and phosphoric anhydride,¹²² and by heating the hydrocarbon at

160° for nine hours with five times its weight of fuming sulfuric acid containing 40% SO₃.¹²³ The sulfonation of naphthalene-1,3,5- and -1,3,7-trisulfonic acids with oleum leads to the formation of naphthalene-1,3,5,7-tetrasulfonic acid.¹²⁴

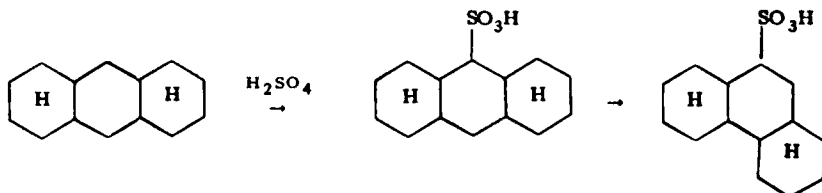
1-Methylnaphthalene, treated with sulfuric acid at room temperature for 5 to 6 hours, gives the 4-sulfonic acid in good yield.¹²⁶ *2-Methylnaphthalene*, heated at 90-100° with sulfuric acid, is converted to the 6-sulfonic acid.¹²⁷ Chlorosulfonic acid converts 1-methylnaphthalene into the 4-sulfonic acid, while 2-methylnaphthalene is stated to give the 8-sulfonic acid.¹²⁸

Alkylated naphthalenesulfonic acids are formed when naphthalene is subjected to the action of chlorosulfonic acid in the presence of alcohols.¹²⁹ Alkylation of the sulfonated naphthalene may be brought about, following sulfonation, by use of alcohols or unsaturated hydrocarbons.¹³⁰

Tetralin, subjected to the action of sulfuric acid, is converted almost exclusively to the 2-sulfonic acid, which crystallizes from water as the dihydrate.¹³¹ With chlorosulfonic acid, both 1- and 2-sulfonic acids are obtained. The 1-sulfo compound may be separated from the 2-acid by taking advantage of the lower solubility of the former in chloroform, or of its lead salt in water.

Anthracene may be sulfonated with sulfuric acid of 53° Bé at 120-135°, giving largely the 2-sulfonic acid. Concentrated sulfuric acid favors the formation of an isomeric sulfonic acid. A mixture in equal amounts of the 1- and 2-sulfonic acids is obtained when the hydrocarbon is sulfonated with an acetic acid solution of oleum or chlorosulfonic acid. The 2-acid may be separated from the 1-acid by precipitation of the former as its sparingly soluble sodium or barium salt.¹³² The presence of mercury favors the formation of the 1-sulfonic acid.¹³³ Sulfonation of anthracene with pyridine-sulfur trioxide complex in pyridine solution at 115° gives largely the 1-sulfonic acid, while sulfonation with the same reagent in a high-boiling petroleum fraction at 165-170° results in the formation, largely, of the 2-sulfonic acid.¹³⁴ Anthracene, heated at 140-145° for five to six hours with 1.4 parts of sodium bisulfate, gives a monosulfonic acid.¹³⁵ Anthracene does not undergo sulfonation in the meso, or 9 and 10 positions.

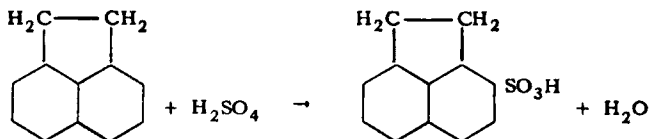
The behavior of octahydroanthracene on sulfonation is comparable to that of 1,2,4,5-tetramethylbenzene: a monosulfonic acid is originally formed on treatment with strong sulfuric acid, but rearrangement occurs on standing, and the compound is converted to octahydrophenanthrenesulfonic acid.¹³⁶



Phenanthrene, heated at or somewhat below 100° with concentrated sulfuric acid, gives a mixture of the 2-, 3- and 9-sulfonic acids.¹³⁷ These isomeric acids have been separated from the mixture by the fractional crystallization of their ferrous and potassium salts.¹³⁸ Phenanthrene has been sulfonated to a mixture of the 2- and 3-sulfonic acids by treatment with an equimolecular amount of chlorosulfonic acid in boiling chloroform.¹³⁹ Disulfonation of phenanthrene results in the formation of a complex mixture containing twelve or more isomeric bodies.¹⁴⁰

Fluorene, treated with a solution of sulfuric or chlorosulfonic acid in chloroform, gives fluorene-2-sulfonic acid.¹⁴¹ Further sulfonation with chlorosulfonic acid, or with four parts of sulfuric acid at 100° results in the formation of the 2,7-disulfonic acid.¹⁴²

Acenaphthene, heated with sulfuric acid at 100°, gives the 3-sulfonic acid.¹⁴³



Heating with a half molecular proportion of chlorosulfonic acid at 125-130° for ten hours results in the formation of the 3,3'-sulfone. The 5-sulfonic acid is obtained when the hydrocarbon is treated at 0° with chlorosulfonic acid.¹⁴⁴

Pyrene yields the 3-sulfonic acid in good yield when treated at 0°-5° with chlorosulfonic acid in carbon tetrachloride or tetrachloroethylene solution.¹⁴⁵

Sulfonation of Phenols

Phenol is readily sulfonated even with cold concentrated sulfuric acid. The *ortho* sulfonic acid is formed in larger proportion at low temperatures; formation of the *ortho* isomer is favored also when a more dilute sulfuric acid is used.¹⁴⁶ Under the most favorable conditions, however, not more than 40% of the *ortho* sulfonic acid is obtained. At lower temperatures, especially in the neighborhood of 0°, an appreciable amount of phenyl hydrogen sulfate is formed. The *para*-sulfonic acid is obtained in 87% yield when the sulfonation is carried out at 100°. Above 160° a certain amount of bis-(*p*-hydroxyphenyl)sulfone is formed, unless an excess of the sulfonating agent is present. Phenol may be sulfonated quantitatively by treatment with a solution of one molecular equivalent of sulfuric acid in a mixture of acetic acid and acetic anhydride.¹⁴⁷

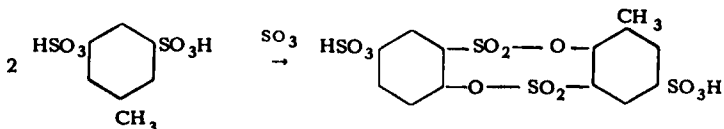
Disulfonation of phenol may be brought about by heating the compound at 100° with a large excess of sulfuric acid.¹⁴⁸ Sulfonation with a mixture in equal amounts of oleum and sulfuric acid also results in the formation of the disulfonic acids.¹⁴⁹ On sulfonating phenol at 120° with ten times its weight of 20% oleum, *phenol-2,4,6-trisulfonic acid* is obtained in 80% yield, together with some disulfonic acid.¹⁵⁰

Treatment of potassium phenol-*p*-sulfonate at room temperature with chlorosulfonic acid results in the formation of 2,4-disulfonic acid, unless an excess of the chlorosulfonic acid is present, in which case the product is phenol-2,4-disulfonyl chloride.¹⁵¹

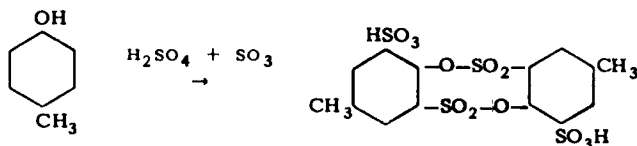
The behavior of *homologs of phenol* on sulfonation is similar to that of phenol. The *ortho* sulfonic acid is formed in larger proportion when the sulfonation is carried out at a low temperature. The *para* isomer predominates when the reaction is carried out at a higher temperature.

o-Cresol is converted to the 4,6-disulfonic acid when heated at 100° with an excess of oleum.¹⁵² Heating with one-half part of 8% oleum at 160-180° for 3 hours under reflux results in the formation of bis-(4-hydroxy-3-methylphenyl)sulfone.¹⁵³ The sulfone,

heated at 160-170° with excess oleum, is converted to the 4,6'-disulfonic acid. A sulfonylide is formed when *o*-cresol is heated at 100° for a few minutes with 1.5 parts 95% sulfuric acid, then for several hours with 13.5 parts of 25% oleum:¹⁵⁴



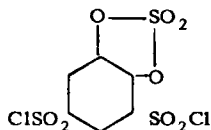
p-Cresol is converted to the 2-sulfonic acid when heated at 100° with an equal weight of sulfuric acid or 6% oleum.¹⁵⁵ Heated with 15 times its weight of 20% oleum, *p*-cresol is converted to a sulfonylide in 87% yield:¹⁵⁶



m-Cresol is converted partially to the 6-sulfonic acid when heated at 100° with sulfuric acid.¹⁵⁷ The 4-sulfonic acid is formed when the phenol is heated at 100° with an equivalent of chlorosulfonic acid in carbon tetrachloride solution, while with two or three equivalents of chlorosulfonic acid, the 4,6-disulfonic acid is obtained. A sulfonylide is formed on heating the mixture at 110°. *m*-Cresol fails to form a sulfonylide when heated with oleum.

2,4-Dimethylphenol and 3,4-dimethylphenol (*asym o*-xylenol) give sulfonylides in appreciable yield when treated with chlorosulfonic acid.¹⁵⁸ Sulfonylides are not formed when the hydroxyl group in a methylated phenol is situated between two methyl groups. 3,4-Dimethylphenol gives the 2,5-disulfonyl chloride when treated with chlorosulfonic acid, while 2,5-dimethylphenol (*p*-xylenol) gives the 3,6-disulfonyl chloride.

Catechol is converted to the 4-sulfonic acid when subjected to the action of sulfuric acid at room temperature or at 100°.¹⁵⁹ The 3,5-disulfonic acid is obtained when the phenol is heated at 100° with 30% oleum, or is treated with chlorosulfonic acid at room temperature.¹⁶⁰ At 150° the phenol gives with chlorosulfonyl chloride a cyclic sulfate of the disulfonyl chloride,



Treatment of *resorcinol* at room temperature with an equimolecular amount of sulfuric acid produces the 4-sulfonic acid.¹⁶¹ The 2,4-disulfonic acid is obtained when *resorcinol* is heated at 100° with oleum.¹⁶² Ammonium *resorcinol*-4-sulfonate, heated with sulfuric acid, gives the 4,6-disulfonate.¹⁶³ Heating the 4,6-disulfonic acid at 200° with oleum gives the 2,4,6-trisulfonic acid.¹⁶⁴

The monosulfonic acid of *hydroquinone* is obtained when the phenol is heated at 50° with a mixture of sulfuric acid and oleum.¹⁶⁵ A hydroquinone disulfonic acid is formed when hydroquinone is heated at 100-110° for an hour with oleum or sulfuric acid.¹⁶⁶

Pyrogallol, or 1,2,3-trihydroxybenzene, heated at 100° with sulfuric acid or pyrosulfuric acid, gives the 4-sulfonic acid.¹⁶⁷

Phloroglucinol, or 1,3,5-trihydroxybenzene, has been monosulfonated by treatment with the theoretically required amount of pyrosulfuric acid.¹⁶⁸ A trisulfonic acid is formed when the phenol is treated at room temperature with ten parts of chlorosulfonic acid.¹⁶⁹

As has been indicated, a number of phenols give sulfonylides on reaction with oleum or chlorosulfonic acid. Sulfonylide formation is observed most frequently with phenols which contain substituents in *ortho* or *para* position to the phenolic hydroxyl. The fact that phenolic bodies are apt to form sulfuric esters when subjected to the action of sulfuric acid in the cold has already been pointed out; ester formation takes place most readily with phenolic compounds of complicated structure.

A disulfonic acid is obtained when 4-hydroxybiphenyl is warmed slightly with concentrated sulfuric acid.¹⁷⁰ 2-Hydroxybiphenyl sulfonates in the 5-position.¹⁷¹ Numerous *alkylated* 2-hydroxybiphenyl polysulfonic acids have been prepared, and some have been proposed as wetting agents.¹⁷² 2,2'-Dihydroxybiphenyl gives the 5,5'-disulfonic acid when subjected to the action of sulfuric acid at 50-60°; at 150°, the 3,3',5,5'-tetrasulfonic acid is formed.¹⁷³ 4,4'-Dihydroxybiphenyl is disulfonated when dissolved in sulfuric acid and heated to 100°;¹⁷⁴ the compound is trisulfonated when heated at 100-120° with ten parts of sulfuric acid, and tetrasulfonated when heated at 160-170° with the same amount of sulfuric acid.

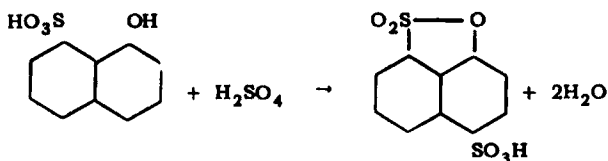
4-Hydroxydiphenylmethane, heated at 100° with a slight excess of sulfuric acid, is sulfonated at the 3-position; with one and one-half parts of sulfuric acid, a disulfonic acid is formed.¹⁷⁵

α -Naphthol gives a mixture of 1- and 4-sulfonic acids when heated at 60-70° with an equal weight of concentrated sulfuric acid.¹⁷⁶ At 50°, with twice the amount of sulfuric acid, the product is the 2-sulfonic acid (Schäffer's *α -acid*), accompanied by the 2,4-disulfonic acid.¹⁷⁷ Sulfonation of *β -naphthol* with concentrated sulfuric acid below 15° results in the formation of the 8-sulfonic acid (Crocein acid) as the principal product; at 80° this is transformed to 2-naphthol-6-sulfonic acid (Schäffer's *β -acid*). The 1-sulfonic acid is obtained by treating *β -naphthol* with 2-2.5 parts of sulfuric acid at -10° for one hour.¹⁷⁸ Initially, the acid sulfuric ester of *β -naphthol* appears to form in this reaction.¹⁷⁹ The 1-acid may be obtained in 80% yield by making provisions for the removal of the acid by crystallization as rapidly as it is formed.¹⁸⁰ The sulfonation of *β -naphthol* is catalyzed by boric acid or sodium borate.¹⁸¹

β -Naphthol may be disulfonated by use of a sufficiently large proportion of sulfuric acid. At 30-35° 2-naphthol-6,8-disulfonic acid (G-acid) is the major product while at 60°, 2-naphthol-3,6-disulfonic acid (R-acid) is the principal product.¹⁸² A mixture of the 3,6- and 6,8-disulfonic acids results on further sulfonating 2-naphthol-6-sulfonic acid. A mixture of the two acids is also formed when *β -naphthol* is heated for a prolonged period at 100-110° with oleum or at 125-150° with sulfuric acid.¹⁸³ These two acids may be separated from their mixtures by making use of the fact that the basic calcium salt of the 3,6-

acid is of lower solubility than that of the 6,8-acid. Conversion to the basic salts may be brought about by the addition of ammonia to the solution of the calcium salts of the acids.

α -Naphthol, heated with oleum below 100° , gives the 2,4-disulfonic acid as the principal product;¹⁸⁴ 2,7- and 4,7-disulfonic acids are formed, together with some 2,4,7-trisulfonic acid, when α -naphthol is heated at 130° with sulfuric acid.¹⁸⁶ 1-Naphthol-5-sulfonic acid is converted to 1-naphthol-2,5-disulfonic acid by heating with sulfuric acid below 100° .¹⁸⁵ 1-Naphthol-8-sulfonic acid is converted to 1,8-naphthosulfone-4-sulfonic acid on treatment with cold oleum, or by heating at 100° with sulfuric acid.¹⁸⁶



β -Naphthol-3,6-sulfonic acid (*R*-acid) has been obtained in 84 to 85% yield by heating β -naphthol with 10% oleum at 120 – 125° for 18 hours.¹⁸⁷ 2-Naphthol-3,6,8-trisulfonic acid is formed when β -naphthol is heated at 140 – 160° with 20% oleum.¹⁸⁸ 2-Naphthol-1,3,6,7-tetrasulfonic acid results on heating sodium 2-naphthol-1-sulfonate with 40% oleum at 130° for 8 hours.¹⁸⁹ Prolonged heating leads to the formation of the corresponding sulfonylide. The 1,6-disulfonic acid is obtained from the sulfonic acid at 30° with about 10% oleum. The 3,6-disulfonic acid gives 2-naphthol-3,6,8-trisulfonic acid on further sulfonation,⁶⁰⁹ and finally the 1,3,6,8-tetrasulfonic acid.⁶¹⁰ 2-Naphthol-7-mono- and -3,7-disulfonic acids give 2-naphthol-1,3,6,7-tetrasulfonic acid.⁶¹¹

Treatment of β -naphthol-7-sulfonic acid with chlorosulfonic acid results in the formation of β -naphthol-1,7-disulfonic acid.¹⁹⁰

2-Naphthol-7-sulfonic acid (*F*-Acid) is obtained from naphthalene-2,7-disulfonic acid by fusion with caustic.

Sulfonation of Phenolic Ethers

The directive influence of the alkoxy group is comparable with that of the hydroxyl group.⁵⁵⁹ Anisole, $\text{C}_6\text{H}_5\text{OCH}_3$, gives the *ortho*-sulfonic derivative when treated with sulfuric acid at ordinary temperature, unless the acid is in large excess (4:1), when *para*-sulfonic and 2,4-disulfonic acids result.¹⁹¹ The *para*-sulfonic acid is formed when the sulfonation is carried out in the presence of acetic acid and acetic anhydride.¹⁹² The principal product obtained on sulfonating phenetole is the *p*-sulfonic acid.¹⁹³ The *para*-sulfonic acid has also been obtained on heating cetyl phenyl ether with concentrated sulfuric acid at 70° .¹⁹⁴ The reaction of chlorosulfonic acid with *p*-cresyl methyl ether gives the 3-chlorosulfonyl-*p*-tolyl methyl ether. Numerous alkylated phenyl ether sulfonic acids have been prepared and proposed as wetting agents and detergents.¹⁹⁵

Catechol monomethyl ether, heated with sulfuric acid at 100° , gives a mixture in equal amounts of 1-hydroxy-2-methoxy-4- and 5-sulfonic acids.¹⁹⁶ The commercial product Thiocol consists of a mixture of the mono and dipotassium salts of these acids. Catechol dimethyl ether (veratrole) gives the 4-sulfonic acid when treated with sulfuric acid or oleum.¹⁹⁷ Sulfonic acids have been prepared from ethers and esters of cresol with high molecular aliphatic alcohols and acids and have been proposed as wetting agents.¹⁹⁸ Methyl and ethyl ethers of hydroquinone give sulfonyl chlorides when treated with chlorosulfonic acid.¹⁹⁹ Sulfonated higher alkyl ethers of hydroquinone have been proposed as wetting agents.¹⁹⁸

1-Naphthyl ethyl ether, reacting with sulfuric acid at ordinary temperature, or at 100°, gives the 4-sulfonic acid.²⁰⁰ The compound is rapidly hydrolyzed with water at 75°. *2-Naphthyl methyl ether*, reacting with chlorosulfonic acid in carbon disulfide solution gives a mixture of the 6- and 8-sulfonic acids; the ethyl ether is first converted to the 1-sulfonic acid, and this undergoes rearrangement to the 6- and 8-sulfonic acids.²⁰¹ The 6- and 8-sulfonic acids are also obtained by treating the ether with sulfuric acid.²⁰²

Sulfonation of Quinones

There appears to be no record of the direct sulfonation of quinones of the benzene and naphthalene series by the action of concentrated or fuming sulfuric acid. It has already been pointed out that sulfonic compounds are formed through the reaction of certain quinones or their derivatives with alkali metal sulfites. While in the resulting sulfonic bodies the quinone structure has been destroyed by reduction, this structure may be restored by oxidation. Quinone sulfonic acids may be made indirectly by the methods employed for the preparation of quinones. The following are offered as examples of some of the diverse methods employed.

Quinone sulfonic acid is obtained through the oxidation of hydroquinone sulfonic acid with lead dioxide.²⁰³ Similarly, *orthonaphthoquinone-4-sulfonic acid* is formed by oxidizing 1,2-dihydroxynaphthol-4-sulfonic acid in acetic acid solution with sodium nitrite.²⁰⁴ This compound is also obtained by oxidizing 2-amino-1-naphthol-4-sulfonic acid with nitric acid.²⁰⁵ 1-Amino-1-naphthol-4-sulfonic acid may be converted to this sulfonated quinone by the action of 20% nitric acid. This method has been utilized for the preparation of a number of other sulfonated naphthoquinones. Thus, *1,4-naphthoquinone-2-sulfonic acid* is formed by oxidizing 4-amino-1-naphthol-4-sulfonic acid with nitric acid,²⁰⁶ and *o-naphthoquinone-3,6-sulfonic acid* is obtained similarly from 1-amino-2-naphthol-3,6-disulfonic acid.²⁰⁷ The 4,6-acid has also been made by this method.²⁰⁸ The *4-monoxime of 1,4-naphthoquinone-2,5-disulfonic acid* results in the form of its sodium salt by boiling the potassium salt of 8-nitronaphthalene-1,6-disulfonic acid.²⁰⁹ 5-Nitro-1,4-naphthoquinone-4-oxime-2,7-disulfonic acid is similarly prepared from 4,5-dinitronaphthalene-2,7-disulfonic acid.²¹⁰

Many of the polycyclic quinones, including among them anthraquinone, may be sulfonated directly by treatment with fuming sulfuric acid.

Anthraquinone cannot be successfully sulfonated with sulfuric acid because of the oxidizing action of the acid at temperatures at which the rate of sulfonation is appreciable.²¹¹ The quinone may be sulfonated, however, by use of fuming sulfuric acid. If monosulfonation is the objective, it is necessary to carry out the reaction under the mildest possible conditions, and to employ a deficiency of the sulfonating agent, so that not more than 50% of the quinone is sulfonated. The sulfonic group enters the β -position, unless a mercury salt is present, when the sulfonic group enters the α -position.

This result may be accomplished by using about 70% of the quantity of free sulfur trioxide required by theory. Of the total anthraquinone employed, 32% is then converted to the monosulfonic acid, 16% to the 2,6- and 2,7-disulfonic acids, and about 2% to hydroxy sulfonic acid.²¹²

A satisfactory procedure for the preparation of anthraquinone-2-sulfonic acid is to add anthraquinone to 1.4 parts of 30% oleum and to heat the mixture for six hours. The

sulfonic acid is recovered in 64% yield by pouring the reaction mixture into water, and adding sodium chloride to the filtered solution of the sulfonic acid.²¹³

Sulfonation of anthraquinone to the 1-sulfonic acid is best brought about by heating anthraquinone at 130°-150° with an equal weight of 20-25% oleum in the presence of mercuric sulfate. The amount of the latter compound generally employed is 1% of the quantity of the anthraquinone.²¹⁴ A satisfactory procedure for the preparation of *anthraquinone-1-sulfonic acid* is to heat 4 parts of anthraquinone with an equal part of 20% oleum and 0.04 to 0.08 part of mercuric oxide, at 130°-135°, to add 1 part of 60% oleum in the course of one hour and to continue heating for an additional hour. The mixture is finally poured into 40 parts of water and potassium chloride is added to precipitate the potassium salt of the 1-sulfonic acid.²¹⁵ The compound is obtained by this method in 63% yield.

Disulfonation of anthraquinone in the absence of a catalyst is best carried out by use of a 110% excess of 40% oleum at 190°, giving an 85% yield of the sulfonated bodies, consisting principally of 2,6- and 2,7-disulfonic acids.²¹⁶ These two isomers are present in the mixture in the ratio 1:1.15. If the reaction is conducted at 20°, 26% of the 2,6- and 52% of the 2,7-isomers are formed.

The disulfonation of anthraquinone in the presence of mercury catalyst is best carried out by heating at 120° for 12 to 15 hours with sufficient 40% oleum to assure the presence of 5 to 10% excess of sulfur trioxide in the reaction mixture.²¹⁷ The temperature of the mixture is raised gradually in order to minimize the oxidative effect of sulfur trioxide. The reaction product is of a complex nature; it consists of 45-50% of the 1,5-disulfonic acid, 24-27% of the 1,5-acid, 15-21% of the 1,7- acid and 5% of the 1,6-acid.²¹⁸ Sulfonation of anthraquinone monosulfonic acid proceeds satisfactorily with sulfuric acid containing more than 3% sulfur trioxide.

Further sulfonation of anthraquinone-1-sulfonic acid with 40% oleum in the absence of a catalyst results in the formation of 68% of the 1,6- and 32% of the 1,7-disulfonic acids. The 1,6- and 1,7- acids are formed also when the 2-sulfonic acid is sulfonated in the presence of mercury catalyst; in this case 59% of the 1,7- acid, and 41% of the 1,6- acid are formed.²¹⁹ Anthraquinone-1-sulfonic acid, sulfonated in the presence of mercury gives the 1,5- and 1,8-disulfonic acids.

It is not possible to introduce three sulfo groups into the molecule of anthraquinone by any of the known methods of sulfonation. Conditions under which the formation of trisulfonic acids may be expected, lead to the formation of anthraquinonehydroxydisulfonic acids.²²⁰ This fact has been utilized, however, for the preparation of industrially important hydroxylated sulfonic acids of hydroquinone. In preparing such compounds, boric acid is usually added to stabilize the hydroxy compounds formed, and to prevent their oxidation.

Hydroxyanthraquinones are successfully sulfonated with oleum at temperatures in excess of 100°. Substitution takes place at position *ortho* to the hydroxyl group.²²¹ *Aminoanthraquinones* are also sulfonated in the *ortho* position to the amino group.²²² *1-Aminoanthraquinone*, for example, gives the 2-sulfonic acid when heated at 210-240° with oleum containing some sodium sulfate, or with chlorosulfonic acid. *2-Aminoanthraquinone*, heated with oleum in the presence of boric acid, gives the 3-sulfonic

acid.²²³ 1-Aminoanthraquinone and its N-methyl derivative, treated with 80% oleum at 30°-35° in the presence of boric acid, undergo both sulfonation and oxidation.²²⁴

Fluorenone, heated at 250-260° with sulfuric acid, gives the 2,7-sulfonic acid.²²⁵

Benzanthrone reacts quantitatively when heated with 30% oleum at 150° for 6 hours, giving the α -sulfonic acid in 81% yield, together with 19% of the β -acid. These may be separated by making use of the differences in solubilities of their barium salts.²²⁶

1,2-Benzanthraquinone has been converted to the 4-sulfonic acid by treatment with 20% oleum. This quinone is more reactive than anthraquinone, and may be sulfonated by heating at 100° with 95% sulfuric acid.²²⁷

Sulfonation of Aromatic Aldehydes and Ketones

Despite the great susceptibility of aromatic aldehydes to oxidation, it is possible to sulfonate these compounds with oleum, or even with sulfuric acid. Benzaldehyde is sulfonated readily with oleum at 50°, the sulfonic group entering the *meta* position.²²⁸

4-Hydroxybenzaldehyde, heated at 65° with oleum, gives the 3-sulfonic acid.²²⁹ The monosulfonic derivative of *o*-hydroxybenzaldehyde can be prepared directly from *meta* amino benzaldehyde by sulfonation and replacement of the amino group by a hydroxyl group via the diazo compound.

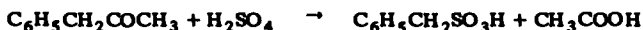
2-Chlorobenzaldehyde undergoes sulfonation with oleum at room temperature, the sulfonic group entering the 4-position, while the 4-chloro compound is unaffected at 80°.²³⁰ 4-Bromobenzaldehyde has been converted to the 3-sulfonic acid by heating at 150° with seven parts of 18% oleum.²³¹

Benzaldehyde-2,4-disulfonic acid has been obtained by heating 2,4-dichlorobenzaldehyde with aqueous sodium bisulfite at 190°-200° for 9 to 10 hours in an autoclave.⁵⁸ Under the same conditions, 2,5-dichlorobenzaldehyde gives 3-chlorobenzaldehyde-2-sulfonic acid.⁵⁹

Aromatic ketones may also often be successfully sulfonated under the proper conditions. Acetophenone is converted to acetophenone-3-sulfonic acid by heating at 100° for 30 minutes with 4 parts of pyrosulfuric acid.²³³ If the temperature is not properly controlled during the addition of acetophenone to the acid, benzoic acid and benzenesulfonic acid may form.

On heating acetophenone at 100° for half an hour with 10 parts of chlorosulfonic acid, acetophenone-2, ω -disulfonyl chloride is obtained.²³²

Methyl benzyl ketone, heated with pyrosulfuric acid, gives a sulfonic acid.²³³ The ketone is cleaved to phenylmethanesulfonic acid and acetic acid when heated with sulfuric acid:²³³



Benzophenone has been converted to benzophenone-3,3'-disulfonic acid by heating at 90° with 10 parts of 15% oleum.²³⁴ *Dimethylaminobenzophenone* has been converted to the 3-sulfonic acid by heating at 130° with oleum.²³⁵

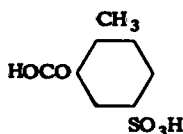
Sulfonation products of alkyl desoxybenzoins of the type $\text{C}_6\text{H}_5\text{CHRCOC}_6\text{H}_5$, in which R is an alkyl group containing 16 to 18 carbon atoms have been proposed as wetting agents.²³⁶

Sulfonation of Carboxylic Acids

Benzoic acid and its simpler derivatives may be sulfonated with 20% oleum at 180-200°.²³⁷ Sulfonation may be effected also in this temperature range by

use of concentrated sulfuric acid to which a little iodine has been added. The *meta* sulfonic acid constitutes 80 to 96% of the sulfonic acids formed. The acid may be isolated as its sodium salt by pouring the reaction mixture into a saturated aqueous solution of sodium chloride, boiling, and then cooling, whereupon, the sodium salt crystallizes out. Benzoic acid is converted to *m*-chlorosulfonylbenzoic acid on heating at 125° with chlorosulfonic acid.²³⁸ Heated at 250° with a mixture of 70% oleum and phosphorus pentoxide in a sealed tube, benzoic acid is converted to 3,5-disulfonic acid.²³⁹

o-Toluic acid, heated for 2 to 3 hours at 160° with five times its weight of concentrated sulfuric acid, gives the *meta* sulfonic acid;²⁴⁰



o-Toluic acid also yields a 3-sulfonic acid under the same conditions. *m*-Toluic acid, heated at 180° with sulfuric acid, gives principally 3-sulfo-5-methylbenzoic acid, with small amounts of the 2- and 4-sulfonic acids.²⁴¹

Cinnamic acid gives the *para* sulfonic acid as the principal product when sulfonated with oleum, with smaller amounts of the *meta* acid.²⁴²

In the sulfonation of phenol carboxylic acids, the hydroxyl group exerts the predominant directive effect, and the sulfonic group first enters the *para* and the *ortho* position to the hydroxyl group.⁵⁵⁸

Salicylic acid is sulfonated in the position *para* to the hydroxyl group when treated with two parts of sulfuric acid containing 3% of sulfur trioxide. The sulfonic acid crystallizes out on standing.²⁴³ With chlorosulfonic acid at 75°, salicylic acid yields 5-chlorosulfonylsalicylic acid; at 180° and with an excess of chlorosulfonic acid, a disulfonic derivative is obtained.²⁴⁴ *m*-Hydroxybenzoic acid, treated with sulfur trioxide, sulfonates in the *ortho* position to the hydroxyl group.²⁴⁵ This acid gives the 2,4,6-trisulfonic acid when heated at 250° for eight hours with a mixture of 50% oleum and phosphorus pentoxide.²⁴⁶ A monosulfonic acid has been prepared from *p*-hydroxybenzoic acid by heating at 100° with five parts of sulfuric acid, or with one molecular equivalent of sulfur trioxide.²⁴⁷

p-Bromobenzoic acid has been sulfonated quantitatively by heating at 120-130° for eight hours with sulfuric acid.

Phthalic anhydride, in common with all derivatives of benzene with two *meta* directing substituents, is sulfonated with great difficulty. 4-Sulphthalic anhydride results in good yield only when phthalic anhydride is heated at 190°-210° with sulfur trioxide for 66 hours.²⁴⁸ Isophthalic acid has been sulfonated to the *sym*-sulfonic acid by reaction with sulfuric anhydride.²⁴⁹ This acid has also been sulfonated by heating at 200° for six hours with oleum.²⁴⁹ Terephthalic acid has been successfully sulfonated by heating at 250°-260° under pressure with oleum.²⁵⁰

1-Naphthoic acid reacts with oleum or 98% sulfuric acid at 60-70° to form a mixture of the 5-, 6-, and 7-monosulfonic acids.²⁵¹ 2-Naphthoic acid, heated at 100° with 98% sulfuric acid, gives 5-sulfo-2-naphthoic acid, together with smaller amounts of the 7- and 8-sulfonic acids.²⁵²

1-Hydroxy-2-naphthoic acid, reacting with oleum, gives first the 4-sulfonic acid, then

the 4,7-disulfonic acid.²⁵³ 2-Hydroxy-1-naphthoic acid, treated with oleum at 20°, gives the 6-sulfonic acid.²⁵⁴ 2,3-Hydroxynaphthalene-8-sulfonic acid is formed in 80 to 85% yield through the sulfonation of 2-hydroxy-3-naphthoic acid with monohydrate at 20% for 24 hours.⁶¹² 2-Hydroxy-3-naphthoic acid, heated for 12 hours at 60° with 3.4 parts of sulfuric acid or weak oleum, gives a mixture of the 6- and 8-sulfonic acids;²⁵⁵ further sulfonation with oleum at 120° yields the 6,8-disulfonic acid. The 6-sulfo acid is formed with the calculated amount of sulfuric acid in boiling chlorobenzene. 1-Hydroxy-4-naphthoic acid sulfonates at the 2-position when treated with sulfuric acid.²⁵⁶ Treatment of 2-hydroxy-3-naphthoic acid with chlorosulfonic acid at a low temperature leads to the formation of the 1-sulfonic acid.²⁵⁷ 2-Hydroxy-6-naphthoic acid gives the 1 and 3-sulfonic acids.

1,8-Naphthalic anhydride, heated at 90° with a large excess of 25% oleum, is converted to the 3-sulfonic acid.²⁵⁸ At 200-230° a disulfonic acid is formed.

Sulfonation of Aromatic Amines

Aromatic amines are sulfonated by sulfuric acid at comparatively high temperatures. Sulfonation may be effected by heating the sulfate of the amines. This method, known as the "Baking Process", has been considered in the section dealing with methods of sulfonation. Amines may be sulfonated also by means of fuming sulfuric acid, and with chlorosulfonic acid. The products obtained by the "Baking" process and by sulfonation with fuming acid are the *para*-sulfonic derivatives, unless the *para* position in the molecule is occupied by a substituent, in which case the sulfonic group enters the *ortho* position. In carrying out the sulfonation with chlorosulfonic acid, the amine is usually dissolved in four times its weight of tetrachloroethane, and a 5% excess of the chlorosulfonic acid over the theoretically required amount is added.

Ortho sulfonic derivatives are generally obtained by the action of chlorosulfonic acid on the aromatic amine. *Meta* sulfonic acids are usually prepared by nitrating the appropriate aromatic sulfonic acid and converting the nitro group to an amino group by reduction.

A quantitative method is available for distinguishing between *ortho*, *para*, and *meta* sulfonation, based on the fact that bromine is capable of replacing *ortho* and *para* sulfonic groups but not the *meta*.²⁵⁹

Aromatic amino sulfonic acids containing an equal number of sulfonic and amino groups are, in general, so little soluble in water, and particularly in dilute sulfuric acid, that they are almost completely precipitated on dilution of the sulfonation mixture.

Aniline may be converted to *sulfanilic acid* by heating at 80-90° with strong sulfuric acid. For the large-scale preparation of *sulfanilic acid*, however, the most economical process consists in heating aniline acid sulfate at 180° for eight hours.²⁶⁰ The compound may be obtained also by heating the aniline salt of ethyl hydrogen sulfate.²⁶¹ Aniline is sulfonated in *ortho* position with cold sulfuric acid.⁵⁵⁷ Oleum causes *meta* substitution in proportion to its SO₃ content. Aniline is generally disulfonated in two steps: the base is first converted to *sulfanilic acid*, and this is heated with oleum at 160-180° five to seven hours. The product formed is *aniline-2,4-disulfonic acid*.²⁶² *Aniline-2,5-disulfonic acid* has been prepared in an indirect manner, through the reduction of nitrobenzene-2,5-disulfonic acid, which may be obtained, in turn, by heating nitrobenzene-2-chloro-5-sulfonic acid with a concentrated aqueous solution of sodium

sulfite for one to two hours under reflux.²⁶³ Aniline yields a trisulfonic acid when it is heated with a large excess of chlorosulfonic acid.²⁶⁴

Treatment of *o*-toluidine sulfate with 30% oleum below 0° results in the formation, principally, of 3-amino-4-methylbenzenesulfonic acid.²⁶⁵ The base gives 3-methyl-4-aminobenzenesulfonic acid in 78% yield when heated at 180° for ten hours with two molecular equivalents of 20% oleum.²⁶⁶ Further sulfonation with oleum at 150-170° leads to the formation of 4-amino-3-methylbenzene-1,5-disulfonic acid.²⁶⁷ The 3-amino-4-methyl acid yields 4-methyl-5-aminobenzene-1,2-disulfonic acid when heated at 160° with chlorosulfonic acid. *m*-Toluidine gives the 6-sulfonic acid in good yield on heating at 125° with 20% oleum for eight hours, further sulfonation giving the 4,6-disulfonic acid.²⁶⁸



p-Toluidine is converted to 2-methyl-5-aminobenzenesulfonic acid when treated with 50% oleum at 0°, or when heated with 2.5 parts of 4% oleum at 180°.²⁶⁹ 2-Amino-5-methylbenzenesulfonic acid is obtained as the principal product if heating is continued until the odor of sulfur dioxide appears.²⁷⁰ Longer heating converts this to 2-amino-5-methylbenzene-1,3-disulfonic acid.²⁷¹ The latter has been made also by heating the monosulfonic acid with chlorosulfonic acid at 140-160°.²⁷² The 1,4-disulfonic acid is obtained on further sulfonating the 2-methyl-5-amino acid with chlorosulfonic acid or oleum. The two isomeric monosulfonic acids may be separated from their mixtures by making use of the differences of the solubilities of the free acids in alcohol, or of their lead salts in water.²⁷³

Asym-m-xylidine, in the form of its sulfate, heated strongly under vacuum, is converted to 1,3-dimethyl-4-aminobenzene-5-sulfonic acid.²⁶ Conversion does not take place successfully if the sulfate is heated under atmospheric pressure.

Acetanilide, subjected to the action of sulfuric acid or oleum in acetic anhydride solution, is converted to the sulfonic acid.²⁷⁴ Heated at 60° for two hours with a molecular equivalent of chlorosulfonic acid, it gives the 4-sulfonyl chloride in high yield.²⁷⁵ Sulfonic acids derived from anilides of long-chain fatty acids are surface active agents of value as wetting agents or detergents.²⁷⁶

1,2-Diaminobenzene hydrochloride, heated at 100° with 7.5 parts oleum, is converted to the 4-sulfonic acid;²⁷⁷ 1,3-diaminobenzene hydrochloride also gives the 4-sulfonic derivative on heating at 170° with the same reagent. 1,4-Diaminobenzene sulfate, heated at 140° with four times its weight of 25% oleum, gives a disulfonic acid.²⁷⁸ 2,4-Diaminotoluene, heated at 100° with oleum, sulfonates in the 5-position.²⁷⁹

Aminophenols undergo sulfonation in *ortho* and *para* position to the hydroxyl group in the presence of an excess of the sulfonating agent. This holds true also of the acyl derivatives of amino phenols. The "Baking" process, on the other hand, applied to *p*-anisidine or *p*-phenetidine, or their chloro derivatives, yields acids in which the sulfo group is in *ortho* position to the amino group.²⁸⁰ *o*-Aminophenol is converted with oleum to its 4-sulfonic acid.²⁸¹ *p*-Aminophenol is converted to the 2-sulfonic acid in 92% yield by heating with sulfuric acid.²⁸² Sulfonation may also be effected by use of oleum. 3-Aminophenol gives the 6-sulfonic acid when heated at 100° with three parts of sulfuric acid.²⁸³ *o*-Anisidine is converted to the 4-sulfonic acid by oleum.²⁸⁴ *p*-Anisidine is demethylated to a large extent, and sulfonated when heated

at 100° with sulfuric acid; with 20% oleum at 55°, on the other hand, 4-aminoanisole-2-sulfonic acid is obtained in high yield.²⁸⁵

Sulfonation of chloroanilines gives the corresponding *o*- and *p*-sulfonic acids; chlorinated toluidines are also sulfonated at *o*- and *p*-positions to the amino group. The sulfonic group enters the 4-position to the amino group in 2-nitroaniline, and the 2-position in 4-nitroaniline.⁶¹³

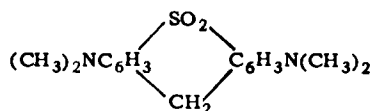
4-Aminobiphenyl is monosulfonated on heating at 130° with four parts of sulfuric acid.²⁸⁶ Acetyldiphenylamine is monosulfonated when treated with oleum at 45°, while disulfonation occurs on heating at 120°.²⁸⁷ 3-Hydroxydiphenylamine gives the 4-sulfonic acid when heated at 100° with sulfuric acid, while in the cold the 3-sulfonic acid is formed.²⁸⁸

Benzidine-3-monosulfonic acid is obtained by heating benzidine with two parts of 100% sulfuric acid at 170° for 1½ hours. The monosulfonic acid precipitates out when the reaction mixture is poured into water.²⁸⁹ The compound has also been obtained by heating the acid sulfate of the base containing a little excess sulfuric acid at 170° for 24 hours.²⁹⁰ Baking the acid sulfate at 210-220° for 36 to 48 hours results in the formation of the 3,3'-sulfonic acid in 90% yield. The 3,3'-disulfonic acid also results when benzidine is heated with two parts of oleum at 170°.²⁹¹ The mono- and disulfonic acids may be separated from their mixture by making use of the fact that the former is insoluble in dilute acetic acid. Benzidine sulfone is formed as the main product with 40% oleum on one hour's heating at 100°.⁵⁶⁵

Roaniline has been converted to mono- and disulfonic acids by heating a mixture of its sulfate with sand at 180°-200°.²⁹² The compound has been sulfonated also by heating it with sodium or potassium bisulfate.²⁹³ A sulfonic acid has been made by heating roaniline with 3 parts of anhydrous metaphosphoric acid and 7 parts 100% sulfuric acid at 120°-130°. Sulfonation with chlorosulfonic acid proceeds at room temperature.²⁹⁴

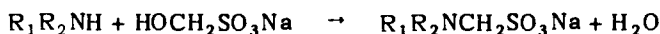
N-Alkylated aromatic amines tend to give *meta* sulfonic acids when treated with sulfonating agents at relatively low temperatures.²⁹⁵ Thus, *methylaniline*, treated at 50° with oleum, give an appreciable amount of the 3-sulfonic acid, though sulfonation at higher temperatures results in the formation of the 4-sulfonic acid.²⁷⁶ Ethylaniline behaves in a similar manner.²⁹⁶ Long-chain *N*-alkylaniline sulfonic acids have been proposed as wetting and cleaning agents.³³⁹

In the preparation of the sulfonates of certain *N*-alkylated aromatic amines, small amounts of water may exert a deleterious effect. This is the case with *tetramethyldiaminodiphenylmethane*, which is transformed to a cyclic sulfone,



when subjected to the action of hot sulfuric acid in the presence of a little water. The amine is successfully sulfonated by heating at 110° with 100% sulfuric acid and adding fuming sulfuric acid gradually during the course of the reaction to eliminate the water formed.²⁹⁸

N-Methylated aromatic amines in which the methyl group is sulfonated are formed on heating primary or secondary aromatic amines with an aqueous solution of formaldehyde bisulfite:²⁹⁹



The amine, as a rule, dissolves rapidly in the bisulfite solution. In the case of aniline, *o*- and *p*-toluidine, and many other primary amines, the sulfomethylated amine crystallizes out on cooling the final reaction mixture. The reaction is greatly facilitated in the case of *o*-chloroaniline, *m*-nitroaniline, and similar compounds when it is carried out in an aqueous alcoholic medium. The product may be recovered by removing the alcohol by evaporation, and cooling the residue to crystallization.

These sulfomethylated amines are easily hydrolyzed by hot acids or alkalis to the original amine, formaldehyde, and sulfite.

Formaldehyde bisulfite is made by mixing a 40% aqueous solution of formaldehyde and sodium bisulfite and heating the mixture on the water bath for a short time.

Diphenylamine is sulfonated in the 4-position when heated in chlorobenzene solution at 90° with a half molecular equivalent of chlorosulfonic acid. The amine is readily disulfonated with this reagent at 110°-115°. ³⁰⁰

In the sulfonation of aromatic amines in which a phenyl and a benzyl group are attached to the nitrogen, the sulfonic group enters the aromatic ring of the benzyl group. *Benzalaniline*, however, is sulfonated in the phenyl group directly attached to nitrogen. ³⁰¹

Naphthylamines undergo sulfonation readily under the proper conditions. As with naphthalene, the position occupied by the entering sulfonic group is influenced by the temperature at which sulfonation is effected. The sulfonic group tends to enter the α -position at temperatures below 100°, and the β -position when the reaction is carried out at a temperature in excess of 160°. In spite of the great diversity of the products of direct sulfonation of naphthylamines, the majority of technically important aminonaphthalenesulfonic acids are prepared by indirect methods.

Of the seven possible *1-naphthylaminesulfonic acids*, four have been prepared by the direct sulfonation of the amine. The "Baking" process applied to α -naphthylamine sulfate gives the 4-sulfonic acid (naphthionic acid) in 85 to 95% yield. ³⁰² Conversion of the sulfate to the sulfonic acid is brought about by heating the finely powdered salt at 180° under 10-15 mm pressure for eight hours. The addition of about 3% of oxalic acid to the sulfate is recommended. The sulfonic acid results also when naphthylamine is heated at 200° with potassium hydrogen disulfate. ³⁰³

1-Naphthylamine-2-sulfonic acid in the form of its ammonium salts results when 1-naphthylamine is heated at 180-185° with sulfamic acid. ³⁰⁴ The 2-sulfonic acid is also obtained by heating α -naphthylamine-N-sulfonic acid, $C_{10}H_7NHSO_3H$, at 185°-190° in a current of carbon dioxide; ³⁰⁵ also by heating sodium naphthionate with 2-3 parts of naphthalene at 217° for 3 hours. α -Naphthylamine gives a mixture of 4- and 5-sulfonic acids when heated with oleum. ³⁰⁶ The 5-sulfonic acid is the principal product when α -naphthylamine hydrochloride is dissolved in 20-25% oleum cooled to 0°. ³⁰⁷ A mixture of the 5- and 6-sulfonic acids is formed, together with the 4,7-disulfonic acid when the base is heated at 125-130° with three to five parts of sulfuric acid. ³⁰⁸ Hot absolute alcohol extracts the calcium salt of the 5-acid from the mixture of the dry calcium salts of these acids, and cold methanol extracts the calcium salt of the 4,7-disulfonic acid, leaving behind the salt of the 6-acid.

1-Naphthylamine, treated with oleum at 120° gives a mixture of the 4,6- and 4,7-di-

sulfonic acids.³⁰⁹ These two acids are formed when naphthionic acid is subjected to the action of oleum at 30°, while at 120° the 2,4,7-trisulfonic acid is formed.³¹⁰ 1-Naphthylamine-2-sulfonic acid yields the 2,5-disulfonic acid with oleum; the same acid is also obtained with chlorosulfonic acid.³¹¹ Treatment of 1-naphthylamine-3-sulfonic acid with 20% oleum below 20° results in the formation of the 3,5-disulfonic acid.³¹² The 5-sulfonic acid gives the 2,5,7-trisulfonic acid. The 6-sulfonic acid of the base gives the 4,6-disulfonic acid with oleum at 100-150°; further sulfonation with oleum or chlorosulfonic acid results in the formation of the 2,4,6-trisulfonic acids.³¹³ The 7-sulfonic acid, treated with oleum, gives 1-naphthylamine-4,7-disulfonic acid.³¹⁴ 1-Naphthylamine-8-sulfonic acid is sulfonated in the 4-position when heated at 100° with oleum;³¹⁵ the 2,4,8-trisulfonic acid is formed on further sulfonation.³¹⁶ 1-Naphthylamine-3,6,8-trisulfonic acid is converted to a sulfam, and finally to the sulfam of the tetrasulfonic acid when treated with 25% oleum.³¹⁷

2-Naphthylamine, subjected to the action of concentrated sulfuric acid at ordinary temperature for several days, gives largely the 5- and 8-sulfonic acids.³¹⁸ Heated at 100-105° with 3 to 3.5 parts of concentrated sulfuric acid, the base gives 40% of the 5-acid, 50% of the 8-acid, and 5% each of the 6- and 7-sulfonic acids.³¹⁹ At higher temperatures the proportion of the 6- and 7-sulfonic acids increases; at 160° to 170° these acids are the predominant products, and each is present in almost equal amount in the reaction mixture.³²⁰ At 200-210° with one molecular equivalent of sulfuric acid, the 6-sulfonic acid is obtained.³²¹ The 6-acid is also obtained almost exclusively at 230° with potassium trihydrogen bisulfate.³²² Treatment of 2-naphthylamine with 20% oleum at 70-80° results in the formation of 68-70% of the 5-sulfonic acid, together with about 30% of the 8-acid; and a trace of the 6-acid.³²³ 2-Naphthylamine-1-sulfonic acid is obtained when sulfur trioxide is made to react with 2-naphthylamine in solution in an inert solvent at a temperature not exceeding 90°;³²⁴ when this acid is heated at 80° with 96% sulfuric acid, it undergoes rearrangement to the 5- and 8-sulfonic acids.³²⁵

2-Naphthylamine sulfate, added to 20-30% oleum and heated at 110-140°, is converted to 2-naphthylamine-6,8-disulfonic acid (Amino G-acid). 2-Naphthylamine-6-sulfonic acid is further sulfonated in the 1-position with oleum at 20°.³²⁶ The 5-sulfonic acid gives 5,7-disulfonic acid; 1-sulfonic acid yields 1,5-disulfonic acid exclusively by the same treatment.³²⁷ 2-Naphthylamine-8-sulfonic acid, subjected to the action of oleum at ordinary temperature for a long period, is converted to the 6,8-disulfonic acid,³²⁸ while the 7-sulfonic acid, treated with four parts of cold 25% oleum, gives 5,7-, 1,7-, and 4,7-disulfonic acids.³²⁹ The 8-sulfonic acid gives the 6,8-disulfonic acid.

2-Naphthylamine, treated with about 3.7 parts of 100% sulfuric acid for one hour at 40°, then mixed with 3 parts of 62% oleum and heated at 85-90° for 11 hours, gives naphthylamine-1,5,7-trisulfonic acid, together with about 41% of the 6,8-disulfonic acid. The latter may be separated from the former without difficulty since it is only slightly soluble in water. Boiling the solution of the 1,5,7-trisulfonic acid in dilute acid converts it to the 5,7-disulfonic acid (Amino I-acid).³³⁰ The 1,5,7-trisulfonic acid is formed also by heating 1,5- or 5,7-disulfonic acids with 40% oleum at 100°.³³¹ 2-Naphthylamine-6,8-disulfonic acid, treated with 40% oleum at 80°-90°, gives the N-sulfonic acid; at 120°-130°, the 3,6,8-trisulfonic acid is formed.³³² The 3,7-disulfonic acid, treated at 130° with 40% oleum, gives a mixture of the 3,6,7- and 3,5,7-tri- and 1,3,6,7-tetrasulfonic acids.³³³ The last named is formed also, together with the 3,5,7-trisulfonic acid, when 2-naphthylamine-1,3,7-trisulfonic acid is heated with 10-20% oleum. The tetrasulfonic acid is also obtained by treating the 3,6,7-trisulfonic acid with oleum. 4,6,8-Trisulfonic acid is formed in good yield on heating 4,8-disulfonic acid with 60% oleum at 100° for ten hours, then at 120° for 2 hours.³³⁴

Many naphthylaminesulfonic acids have been prepared from nitronaphthalene-sulfonic acids by reduction. The nitronaphthalenesulfonic acids may be obtained by sulfonating nitronaphthalenes, or nitrating naphthalenesulfonic acids.

Sulfonation of *acetyl-1-naphthylamine* with oleum results in the formation of 4- and 5-sulfonic acids.³³⁵ Sulfonic acids derived from N-alkylated naphthylamines with long chain acyl groups attached to nitrogen have been proposed as wetting agents.³³⁶

1,8-Diaminonaphthalene sulfate yields the 4-sulfonic acid when heated at 100°.³³⁷ *1,5-Diaminonaphthalene* is sulfonated in the 2-position when its sulfate is dissolved in 5% oleum, 25% oleum is added to the solution, and the mass is heated at 100-110°.³³⁸ *N-Acetyl-1,4-diaminonaphthalene* is sulfonated in the 7-position when treated with 20% oleum at 25-30°.³³⁹

8-Amino-1-naphthol gives a mixture of the 2- and 4-sulfonic acids when acted upon with sulfuric acid at 15-20°. The two acids may be separated by making use of differences in the solubilities of their calcium salts.³⁴⁰ When the base is heated at 130-160° with 75% sulfuric acid, it is converted to the 2-sulfonic acid;³⁴¹ further treatment with sulfuric acid at 100° yields the 2,4-disulfonic acid.³⁴² 1-Amino-7-naphthol is converted to the 3-sulfonic acid at 20 to 30° by 100% sulfuric acid.⁵⁶⁴ 1-Amino-2-naphthol gives the 6-sulfonic acid on heating at 60° with 92.5% sulfuric acid for one hour.

8-Amino-1-naphthol gives the 4-sulfonic acid with concentrated sulfuric acid; at 130°-160° it gives the 2-sulfonic acid with 75% sulfuric acid.⁵⁶² 7-Amino-2-naphthol gives a disulfonic acid with 60° Be sulfuric acid at room temperature. Aminonaphthol-disulfonic acids are generally converted to dihydroxynaphthalenedisulfonic acids when heated with dilute acids; the disulfonic acid obtained from 7-amino-2-naphthol gives a hydroxymonosulfonic acid by removal of one sulfonic group. 8-Amino-2-naphthol is sulfonated by concentrated sulfuric acid to the 7-sulfonic acid at 20 to 30° and the 6-sulfonic acid at 95°.⁵⁶³

1-Naphthylmethylaniline, $C_{10}H_7NHCH_3$, is converted to a mixture of 2- and 4-sulfonic acids when treated with sulfuric acid. Further sulfonation results in the formation of the 2,4-disulfonic acid.³⁴³ *1-Naphthylidimethylaniline* is converted to the 5-sulfonic acid and to an isomeric sulfonic acid when it is heated at 130° with sulfuric acid.³⁴⁴

2-Naphthylethylaniline hydrochloride gives the sulfonic acid with oleum at ordinary temperature; with 100% sulfuric at 140° the 7-acid is obtained as the principal product.³⁴⁵

N-Phenyl- and *N-o-tolyl-2-naphthylaniline* are sulfonated in the 5- and 8-positions when treated with four parts of 100% sulfuric acid at ordinary temperature.³⁴⁶

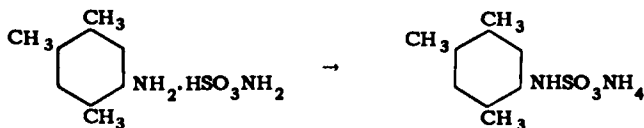
2,7-Diamino- and dianilinophenanthraquinones give sulfonic acids which are mordant dyes.³⁴⁷

Azobenzene is sulfonated by 20% oleum to azobenzene-4-sulfonic acid.⁵⁶⁰ When substituents are present in the aromatic ring, they determine the direction of substitution of the sulfonic group.⁵⁶¹

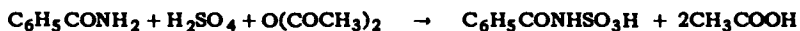
Sulfamic Acids

Aromatic sulfamic acids, $ArNHSO_3H$, are formed through the reaction of primary aromatic bases with chlorosulfonic acid or sulfuric acid in cold chloroform solution.³⁴⁸ Sulfamic acids are also obtained by the reaction of aromatic bases with fluorosulfonic acid.

Pseudocumidine sulfamate is converted to the ammonium salt of pseudocumylsulfamic acid when heated at 160-170°:



Benzamido-N-sulfonic acid results by the action of a mixture of acetic anhydride and sulfuric acid on benzamide:³⁴⁹



Amido sulfonic acid may be obtained also by this method from other acid amides.

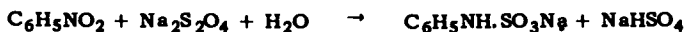
Aromatic nitro compounds, subjected to the action of aqueous solutions of acid sulfites, are converted to sulfamic acids:³⁵⁰



The yield of sulfamic acid increases with increase in the number of alkyl groups attached to the aromatic ring; it is 95% with nitroxylenes. The reaction proceeds more readily with compounds in which the nitro group is in the *para* position to the alkyl group than with those in which the nitro group is in the *ortho* position. Esters of nitrated aromatic carboxylic acids are also converted to sulfamic acids by this treatment, though the free acids give the sulfonic derivatives of the corresponding amino acids.³⁵¹ The rate of reaction is greater in dilute, than in concentrated bisulfite solution. The sodium salts of sulfamic acids generally may be salted out from their weakly acid solution by the addition of sodium chloride.

Sulfamic acids are also formed through the reaction of sodium hydrosulfite with certain aromatic nitro compounds.

Phenylsulfamic acid is obtained, for example, when nitrobenzene is suspended in water containing a little sodium phosphate, and hydrosulfite is added, the temperature rising spontaneously to 65°.³⁵²



Sulfonation of Aromatic Chloro and Nitro Compounds

Halogenated aromatic bodies are sulfonated with greater difficulty than the corresponding hydrocarbons. Halogens exert a strong *para*-directing influence, and the *ortho*-sulfonic acid is formed only when the *para* position is occupied by a substituent. The *para*-directive influence of a halogen supersedes that of a methyl group, but the *ortho*-directive influence of the latter is stronger than that of a halogen atom. Thus, while 2-chlorotoluene gives only the 5-sulfonic acid, 4-chlorotoluene yields a mixture of the two possible isomers, with a

greater proportion of the 2-sulfonic acid. Sulfonating agents which react with difficulty with brominated and iodinated aromatic bodies often cause the removal or rearrangement of the halogen atoms.

Sulfonation of *chlorobenzene* proceeds well with 10% oleum at 60° or lower.³⁵³ Reaction with an equivalent of sulfonic acid results in the formation of the 4-sulfonic acid, together with a little of the chloride of this acid and the sulfone.³⁵⁴

Chlorobenzene heated at 300° with 20% oleum is converted to the 3,5-disulfonic acid; chlorobenzene-4-sulfonic acid and -2,4-disulfonic acid are also converted to the 3,5-acid by this treatment.³⁵⁵

o-Dichlorobenzene gives the 4-sulfonic acid with oleum at room temperature or at 210°.³⁵⁶ *m*-Dichlorobenzene is also sulfonated at the 4-position by oleum of varying composition;³⁵⁷ heating with 45% oleum at 140°-150° for 5 hours gives the 4,6-disulfonic acid.³⁵⁸ *p*-Dichlorobenzene has been monosulfonated by treatment with sulfur trioxide or 10% oleum.³⁵⁹

Monochloroprehnitene gives chloropentamethylbenzene and ψ -cumenesulfonic acid when heated at 60° with sulfuric acid.³⁶⁰ Chlorodurene undergoes a Jacobsen rearrangement when subjected to the action of sulfuric acid at 60°.³⁶¹

2-Chlorobenzaldehyde is sulfonated by oleum at room temperature, while the 4-chloro compound is unaffected at 85°.³⁶²

Bromobenzene undergoes sulfonation normally when treated with oleum, giving the 4-sulfonic acid, together with a little bis-(*p*-bromophenyl)-sulfone;³⁶³ with oleum at 300°, it gives the 3,5-disulfonic acid.³⁶⁴ *Monobromoprehnitene* gives a mixture of dibromoprehnitene and prehnitene when heated with sulfuric acid;³⁶⁵ *monobromo-ψ-cumene* and *monobromodurene* behave in a similar manner.

Iodobenzene treated with sulfuric acid or oleum gives the 4-sulfonic acid, together with a little bis-(4-iodophenyl)sulfone.

Fluorobenzene is converted to the 4-sulfonic acid when treated at 70° with 10% oleum.³⁶⁶

The behavior of halogenated naphthalenes on sulfonation shows certain similarities to that of halogenated benzene hydrocarbons. Chlorine and bromine in the 2-position in the naphthalene nucleus direct the entering sulfonic group to the 6- and 8-positions, while iodine in the 2-position causes the formation of 5- and 8-sulfonic acids. The 8-sulfonic acids undergo rearrangement to the 6-isomer when heated. 1-Halonaphthalenes, sulfonated at a low temperature, give principally the 4-sulfonic acids.

1-Chloronaphthalene gives the 4-sulfonic acid when treated with sulfuric or chlorosulfonic acid in carbon disulfide solution.³⁶⁷ At 160° the 6- and 7-sulfonic acids are formed.³⁶⁸ Further sulfonation of the 4-sulfonic acid with 20% oleum at 100° gives the 4,7-disulfonic acid, while continued sulfonation at 170° results in the formation of the 2,4,7-trisulfonic acid.³⁶⁹ The 6-sulfonic acid gives the 4,6-disulfonic acid on further sulfonation, and the 3-acid yields the 3,5-derivative.³⁷⁰ 2-Chloronaphthalene is converted to the 6,8-disulfonic acid when heated at 160-180° with excess of oleum.³⁶⁷ The 6,8-diacid is also obtained by heating the 6- or 8-acid with pyrosulfuric acid.³⁷¹

9,10-Dichloroanthracene, reacting with chlorosulfonic acid in chloroform solution at 40°, gives the 2-sulfonic acid.³⁷² The 2-sulfonic acid is also obtained on subjecting

the dichloro compound to the action of 100% sulfuric acid at 30°, or of oleum in nitrobenzene solution. The corresponding dibromo compound behaves in a similar manner. The compounds resulting by the action of oleum at 100° are in all probability the 2,6- and 2,7-disulfonic acids.

9-Chloro and 9-bromophenanthrene, reacting with sulfuric acid at 100°, give a monosulfonic acid which is either the 3- or 6-derivative.³⁷³

Dibromofluorene has been converted to a sulfonic acid by the action of chlorosulfonic acid.³⁷⁴

Sulfonation of *nitro derivatives* of benzene and its homologs is of relatively little importance, because nitrated sulfonic acids are usually prepared through the nitration of sulfonic acids, rather than through the sulfonation of nitrated bodies. The reason for this is that sulfonation of nitrated compounds proceeds with greater difficulty than the reverse process of nitration of sulfonic acids. When polynitro compounds are subjected to the action of sulfonating agents, one nitro group is occasionally replaced with a sulfonic group; the other nitro groups may remain intact, or may be removed or reduced to an amino group; or again may be replaced with a hydroxyl group.

A satisfactory *procedure* suitable for the monosulfonation of aromatic nitro compounds is to add the nitrated product to five times its weight of 20-25% oleum and to stir the mixture until a test sample dissolves completely in water. The optimum reaction temperature varies according to the nature of the nitro compound. *p*-Nitrotoluene may be effectively sulfonated at 25-30°; nitrobenzene is best sulfonated at 100°,³⁷⁵ while the most satisfactory temperature range for the sulfonation of *m*-nitroaniline is 130-140°.³⁷⁶ Mercury salts act as catalysts, and are of definite value in the sulfonation of dinitro compounds. The yield of the sulfonic body is not satisfactory when dinitrobenzene is sulfonated in the presence of mercury salts, because considerable charring occurs.³⁷⁷ Explosive decompositions may occur during the sulfonation of nitro compounds. Traces of impurities would seem to lower the explosive temperature considerably. 2,4-Dinitrobenzene decomposes explosively on contact with oleum. Sulfonation of 2-nitro-6-chlorotoluene with 20% oleum should be carried out below 85°.

In many instances the nitrosulfonic acid precipitates out when the reaction mixture is poured into a small amount of water.

2-Nitrophenol is converted to the 4-sulfonic acid by treatment with sulfuric acid or chlorosulfonic acid.³⁷⁸ The compound has been sulfonated successfully by use of a mixture of one part of 100% sulfuric acid with 2.5 parts 25% fuming sulfuric acid. If sulfonation is carried out in the presence of mercury salts, a mixture of sulfonic acids is formed, including *o*-nitrophenyltrisulfonic acid. *m*-Nitrophenol is more resistant to the action of sulfonating agents than either *o*- or *p*-nitrophenol; it has been converted to a monosulfonic acid, however, by heating at 90° for 40 hours with a mixture of 1 part of 100% sulfuric acid and 2.5 parts of 25% oleum.³⁷⁹ *m*-Nitrophenol does not give a sulfonic acid with chlorosulfonic acid. *p*-Nitrophenol yields the monosulfonic acid when treated with 100% sulfuric acid or with oleum; the compound has been sulfonated by adding it to four times its weight of 25% oleum, and keeping the mixture at 0° for 80 hours.³⁸⁰ The yield of sulfonic acid obtained by this method is 45%. Sulfonation with sulfuric acid takes place more readily in the presence of infusorial earth or animal charcoal. Chlorosulfonic acid fails to sulfonate *p*-nitrophenol. The monosulfonic acid of *p*-nitrophenol has been obtained by heating the compound with monopotassium trihydrogen bisulfate first at 120-130°, then at 150°.³⁸¹

Sulfonation of nitronaphthalenes takes place less readily than the reverse process of nitration of naphthalene sulfonic acids, and for this reason nitronaphthalenesulfonic acids are generally prepared by the nitration of the sulfonic acids.

The reaction of *1-nitronaphthalene* with sulfuric acid, oleum, or chlorosulfonic acid results in the formation of a mixture of the 5-, 6-, and 7-sulfonic acids, with the 5-acid predominating.³⁸² *2-Nitronaphthalene*, treated with oleum at a low temperature, gives a mixture of the 5- and 8-sulfonic acids.³⁸³ *1,8-Dinitronaphthalene* gives the 3-sulfonic acid when heated at 100-110° with oleum.³⁸⁴ The *1,5-dinitro* compound, treated in the same manner, is sulfonated in the 3-position.

1-Nitroanthraquinone, heated at 130° with oleum in the presence of mercuric sulfate, gives a mixture of sulfonic acids containing 52% of the 5-acid, 29% of the 8-isomer, 12% of the 7-acid, and 7% of the 6-acid.³⁸⁵

Properties and Reactions of Sulfonic Acids

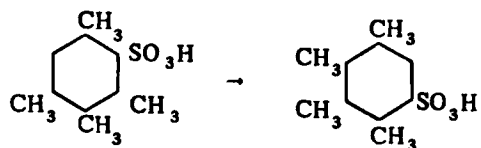
Many aromatic sulfonic acids are highly soluble in water and for this reason are obtained in the crystalline form with difficulty. Their sodium salts are, as a rule, difficultly soluble in saturated sodium chloride, and can therefore be precipitated from their solutions by saturating the latter with sodium chloride. The calcium and other alkaline-earth metal salts of sulfonic acids are generally soluble in water, but differences in their solubility may often be utilized for the separation of various isomeric acids. Aromatic amino sulfonic acids are, as a rule, slightly soluble in cold water. Sulfonyl chlorides derived from certain aromatic acids are crystalline bodies, and may be obtained in a pure form by crystallization. Since the sulfonyl chlorides may be readily converted to the corresponding acid, this property may be utilized for the isolation of the sulfonic acids in the pure form. Certain sulfonic acids may be distilled without decomposition under very high vacuum.³⁸⁶ The sulfonic group in many compounds is replaced with a nitro group on treating them with concentrated nitric acid. Sulfonic acids are, in general, strong acids.

Molecular Rearrangements

Many sulfonic acids undergo isomerization when subjected to heat; the phenomenon is reversible and in general an equilibrium condition is reached at any given temperature and concentration of acid. The effect is utilized for the preparation of the isomeric acids.⁶¹⁴ Rearrangement of *o*-toluenesulfonic acid results in the formation of the para isomer. Many naphthalenesulfonic acids undergo the rearrangement. In the sulfonation of naphthylamine with oleum the 1,5,7-trisulfonic acid undergoes rearrangement to the 3,5,7-acid when treated with an excess of oleum; naphthalenesulfonic acids are not thus affected. Readiness of sulfonic acids to undergo hydrolysis would appear to be related to their readiness to undergo isomerization. In the 1-naphthylaminosulfonic series, ease of hydrolysis decreases in the order 1,8-, 1,4-, 1,5-, and 1,6-acids.

Jacobsen Rearrangement³⁸⁷

Certain aromatic polyalkyl or halo sulfonic acids undergo molecular rearrangement to an isomeric form in the course of sulfonation, or on allowing the sulfonation product to remain in contact with concentrated sulfuric acid for a prolonged period. Typical of the rearrangement is the formation of prehnitenesulfonic acid from durennesulfonic acid:



Vicinal derivatives are formed through the Jacobsen rearrangement, in contrast to the usual orientation rule observed in Friedel-Crafts reaction. It has been established, at least in the case of hydrocarbons, that the rearrangement takes place following the formation of the sulfonic acid, and that the original aromatic body does not undergo rearrangement before being sulfonated.³⁸⁸ The migration may be of intra- or intermolecular nature; in most cases, both types of migrations occur simultaneously. The transformation is not quantitative, but is accompanied by side reactions, the by-products including sulfur dioxide and polymeric bodies.

Substituents capable of migration are the methyl and ethyl groups, halogens, and the sulfonic group. The ease with which the rearrangement takes place is determined by the substituents present in the benzene ring. If only alkyl groups are present in the molecule, the transformation takes place only with the tetra- and pentaalkyl benzenes.³⁸⁹ When halogens and alkyl groups are both present, migration takes place the more readily the greater the number of alkyl groups attached to the nucleus. In the polyalkyl halo benzenes, migration of an alkyl group has been observed only with chlorodurene and chloroisodurene. With certain halo alkyl benzenes, migration of an alkyl group occurs after removal of the halogen by an exchange reaction. In the halobenzenes, migration of a halogen atom has been observed even with monohalogenated derivatives. The rearrangement of halogenated benzenes results in the formation of mixtures of various compounds, from which pure compounds are isolated with difficulty.

Esters of Aromatic Sulfonic Acids

Esters of aromatic sulfonic acids are obtained readily by adding a slight excess of 25% caustic solution to a mixture of the sulfonyl chloride with an excess of alcohol, with cooling, and agitating for several hours.³⁹⁰ The ester separates out as an oily layer, and is withdrawn, washed with water, and dried. Some of these esters may be purified by distillation under vacuum. Even such alkali-sensitive compounds as chlorohydrins may be converted to sulfonic esters by this method. Methyl *p*-toluenesulfonate has been prepared by this method in 92% yield, and the ethyl ester in 85% yield. The reaction of an alcohol with sulfonyl chlorides may be effected also in the presence of pyridine.

Esters of the higher alcohols may be prepared by adding the sulfonic chloride to a solution of potassium hydroxide in the alcohol. A solvent such as acetone may be used. Sulfonic esters may be prepared through the reaction of the chloride with the alkali metal derivative of the alcohol. The general procedure is as follows:

The alkali metal derivative of the alcohol in solution in the alcohol is added gradually and with stirring to the solution of an equivalent of sulfonic chloride in the alcohol or in ether maintained at 20°. When the liquid no longer reacts alkaline, sufficient water is added to dissolve the sodium chloride formed and the organic layer is taken up with chloroform. The extract is washed with water and sodium bicarbonate solution and again with water; it is dried with calcium chloride and the ester is isolated by distillation under vacuum.⁶¹⁵

The method of widest applicability for the preparation of arylsulfonic esters is the reaction of the alcohol with the sulfonyl chloride in the presence of tertiary bases, especially pyridine.⁶¹⁶ The reaction should be carried out under anhydrous conditions. Chlorinated compounds and quaternary ammonium compounds may form in this reaction as by-products; their formation may be avoided to a large extent by carrying out the reaction at 0°. Pyridine shows a tendency to react with the sulfonic esters of lower aliphatic alcohols with the formation of the pyridinium salt of the sulfonic acid.

Arylsulfonic esters of higher alcohols have been obtained in the pure form through the reaction of the sulfonyl chloride with the alcohol in the presence of zinc oxide.⁶¹⁷ Sulfonic esters may be prepared by the reaction of the silver salt of the sulfonic acid with alkyl halides. The reaction may be carried out in solution in acetonitrile, which has a solvent power for the silver salt of aromatic sulfonic acids. Secondary and tertiary halides do not give sulfonic esters, but are dehydrohalogenated.⁶¹⁸ Alkyl esters of sulfonic acids may be obtained also by heating an alkali metal sulfonate at 150 to 160° with an alkyl sulfate. Ethyl benzenesulfonate has been prepared by the reaction of the anhydride of the sulfonic acid with alcohol.³⁹¹

Arylsulfonic esters have been prepared through the reaction of sulfonic acids with aliphatic diazo compounds:⁶¹⁹



Aromatic sulfonic esters may be formed through the reaction of arylsulfonic acids with certain unsaturated compounds.⁶²⁰ Reaction fails to proceed with isobutylene. Hydroxysulfonic esters have been obtained by the reaction of sulfonic acids with ethylene oxide, butene-1-oxide, cyclopentene oxide and cyclohexene oxide.⁶²¹

Aromatic esters of arylsulfonic acids may be obtained through the reaction of arylsulfonic chlorides with phenols or sodium phenolates.⁶²² The reaction between sulfonyl chlorides and phenols may be carried out in the presence of alkali metal hydroxides or carbonates, or tertiary bases.⁶²³ Chlorinated products may form, especially with polynitrophenols, when dimethylamine is used to combine with the hydrogen chloride formed in the reaction. Phenols and sul-

fonyl chloride react readily in alcoholic or acetone solution in the presence of sodium ethoxide or caustic. The phenolic group in aminonaphtholsulfonic acids reacts exclusively with sulfonyl chlorides in strongly alkaline medium.⁶²⁴ The reaction with caustic may be carried out by adding a 25% aqueous caustic to a mixture of the sulfonyl chloride and phenol with cooling. Reaction proceeds well with most types of phenols, including mononitrophenols. Dinitrophenols react with difficulty, however, and trinitrophenols fail to react.

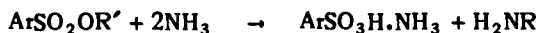
p-Bromobenzenesulfonic esters of phenols may serve for the characterization of the latter. The esters may be prepared by mixing equivalent quantities of the phenol and bromobenzenesulfonyl chloride with four equivalents of pyridine and stirring the mixture for three hours at 15°. The mixture is poured in ice water containing sufficient hydrogen chloride to combine with the pyridine, the precipitated ester is filtered, air dried and purified by crystallization from alcohol.⁶²⁵

An alternative method consists in adding an equivalent of 0.7*N* aqueous sodium hydroxide dropwise in the course of thirty minutes to a mixture of equivalent quantities of the sulfonyl chloride and phenol heated to 60 to 80°. The mixture is maintained at this temperature for an additional hour or two, the ester is filtered, washed and purified by repeated crystallization from alcohol containing a little benzene.⁶²⁶

Behavior of Aromatic Sulfonic Esters

Aryl sulfonic esters undergo hydrolytic cleavage with water, aqueous alcohol or aqueous alkalis.⁶²⁷ Many sulfonic esters are saponified by alkalis in the cold with comparative ease. The most satisfactory method for the decomposition of sulfonic esters into the corresponding acid and alcohol consists in the treatment of the esters with sodium alcoholate in absolute alcoholic solution.

Ammonia reacts with aryl sulfonic esters to form the ammonium salt of the acid and a substituted amine:⁶²⁸



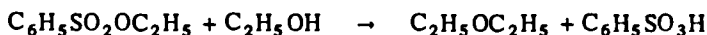
An unsaturated compound may form from sulfonic esters of secondary alcohols:⁶²⁹



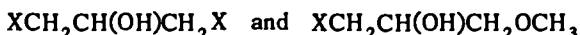
Reaction proceeds in a similar manner with primary and secondary amines and with hydrazines. Hydrazine fails to react with sulfonic esters of tertiary alcohols. Reaction with tertiary bases may result in the formation of quaternary ammonium salts.⁶³⁰

Aromatic esters of arylsulfonic acids are more resistant to hydrolytic agents than the corresponding alkyl esters; they decompose to the phenol and sulfonic piperidide when heated at 100° with piperidine.⁶³¹ 2,4-Dinitrophenyl *p*-toluenesulfonate gives *p*-toluenesulfonic acid and 2,4-dinitrophenyl piperidide when heated with piperidine;⁶³² this ester yields 1-chloro-2,4-dinitrobenzene and the pyridinium salt of the sulfonic acid with pyridine.⁶³³

Alkyl esters of sulfonic acids are capable of reacting with alcohols and phenols to form ethers:



Methyl ethers of halo alcohols of the type

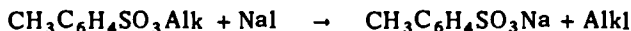


which cannot be obtained by the usual methods, have been prepared from the alcohols by reaction with methyl *p*-toluenesulfonate.³⁹²

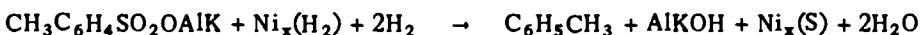
Sulfides are similarly obtained from mercaptans.⁶³⁴ S-Alkylisothiureas are formed by reaction of alkyl esters of *p*-toluenesulfonic acid with thioureas.⁶³⁵

Reactive methylene groups may be alkylated with the alkyl esters of arylsulfonic acids. Reaction is effected with the enolate of the methylenic body.⁶³⁶ Substituted acetylenes have been prepared by this method from the sodium salts of acetylene and monosubstituted acetylenes.⁶³⁷

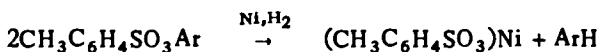
The reaction of inorganic salts with esters of arylsulfonic acids may result in the formation of the ester of the inorganic acid by an exchange of the alkyl or aryl group for the metal of the salt:⁶³⁸



Treatment of alkyl esters of *p*-toluenesulfonic acid at room temperature with hydrogen in the presence of several times their weight of Raney nickel results in the cleavage to toluene, an alcohol and a sulfide:⁶³⁹



Aromatic esters of arylsulfonic acids give an aromatic hydrocarbon and the nickel salt of the arylsulfonic acid:⁶³⁹



Lithium aluminum hydride reacts with *p*-toluenesulfonic esters in boiling ether-benzene mixture, or in tetrahydrofuran, with the formation of a hydrocarbon and, exceptionally, with the formation of an alcohol and a sulfinic acid and other products of reduction.⁶⁴⁰ Arylsulfonic esters of secondary alcohols are decomposed less readily by hydrogenolysis than those of primary alcohols. Aryl esters are cleaved to a phenol and a sulfonic acid and other reduction products.

Aromatic Sulfonyl Chlorides

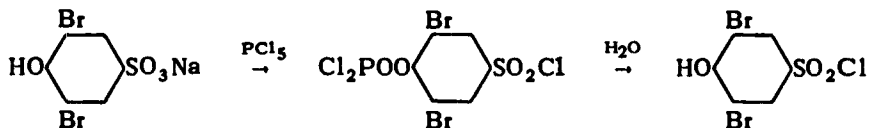
Sulfonyl chlorides are formed through the reaction of sulfonic acids or their salts with phosphorus pentachloride:



The reaction with the free sulfonic acid is carried out as follows: The finely powdered sulfonic acid is mixed with a quantity of phosphorus pentachloride 10% in excess of the theoretical. The mixture is rapidly transferred to a flask and heated under reflux. Reaction often starts spontaneously with considerable evolution of heat. The mixture is heated gently until it no longer gives off vapors of hydrogen chloride. The liquid is

then poured onto ice, and the mass is stirred for a time in order to complete the hydrolysis of the phosphorus oxychloride. The sulfonyl chloride, which separates as a second layer, is then drawn off, washed free from acid, and dried. The yields are generally good.

The method, in general, is not applicable to phenolic compounds, although certain substituted phenol sulfonyl chlorides, such as phenol-2,6-dibromo-4-sulfonyl chloride, have been obtained from the sodium salts of the sulfonic acids.³⁹³ A phosphorus oxychloride ester is first formed, which is decomposed to the sulfonyl chloride on treatment with ice:



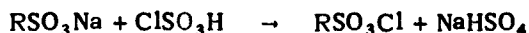
If the hydroxyl group is flanked on both sides by substituent groups, the oxychloride ester is not formed.³⁹⁴ When the phenolic hydroxyl group in a phenol-sulfonic acid is blocked by acylation, reaction with phosphorus pentachloride proceeds normally, giving the acylated phenol sulfonyl chloride.³⁹⁵ Phenol-*m*-sulfonic acid behaves exceptionally, and may be converted to the corresponding sulfonyl chloride by treating its sodium salt with phosphorus pentachloride, and subsequently washing the product with water.³⁹⁶

Sodium phenol-2,4-disulfonate gives chlorobenzene-2,4-disulfonyl chloride when heated with phosphorus pentachloride at 140–150°. ³⁹⁷ A similar behavior is shown by sodium phenol-2,4,6-trisulfonate and resorcinol-4,6-disulfonic acid.³⁹⁸

Anthracene- β -monosulfochloride is obtained through the reaction of the sodium salt of the sulfonate at refluxing temperatures with phosphorus pentachloride in suspension in a mixture of phosphorus oxychloride and glacial acetic acid.⁵⁴¹ α -Naphthol- β -sulfonic chloride is obtained in a similar manner.⁵⁴²

Sulfonyl chlorides may be obtained also by heating the alkali metal salts of sulfonic acids with phosphorus oxichloride, POCl_3 . Treatment of α - and β -naphtholsulfonic acids with this reagent results in the formation of complex condensation products.

Replacement of the hydroxyl group in sulfonic acids may be brought about by heating the sulfonic acids or their salts with 93–96% and occasionally 99% chlorosulfonic acid:³⁹⁹



Many arylsulfonyl chlorides are highly sensitive to water and may decompose when the reaction mixture is poured on ice. Decomposition may be held to a minimum by working rapidly at a low temperature. Removal of the unreacted chlorosulfonic acid with sodium chloride, anhydrous sodium carbonate or a tertiary base, or extraction of the arylsulfonyl chloride with benzene may be successfully effected in special cases.

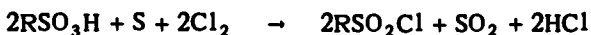
The method is applicable to aminosulfonic acids with ortho substituents, and to some diaminoarylsulfonic acids. Arylamino sulfochlorides are readily prepared by this method. Hydroxyarylsulfonyl chlorides may often be prepared in good

yield from the hydroxysulfonic acids.⁶⁴¹ Aminophenol- and aminonaphtholsulfonic acids cannot, in general, be converted directly to sulfonyl chlorides without the protection of the amino group by acylation.⁶⁴² Occasionally, as with anthraquinone-1-sulfonic acid, the sulfonic group remains intact.

Sulfonation and conversion to the sulfonyl chloride may be accomplished simultaneously by use of a mixture of molecular equivalents of chlorosulfonic acid and oleum. For example, chlorobenzene, mixed with two-thirds its weight of 60% oleum and added to a mixture of chlorosulfonic acid with two-thirds part 60% oleum held at 10° or lower, is converted to *p*-chlorobenzenesulfonyl chloride.⁴⁰⁰

Arylsulfonyl chlorides have been obtained by the action of chlorine water on aromatic sulfonic acids.⁴⁰⁹

Sulfonic acids may be converted to sulfonyl chlorides by reaction with sulfur and chlorine:⁵⁷¹



The reaction may be effected also with sulfuryl chlorides.

Aromatic sulfonyl chlorides are formed by the reaction of phosgene with alkali metal salts of aromatic sulfonic acids in an indifferent solvent such as nitrobenzene at 140–180°.

Arylsulfonic salts may be converted to sulfonyl chlorides by reaction with benzotrichloride:⁶⁴³

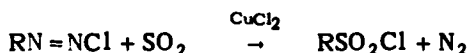


Arylsulfonic chlorides may be obtained by the oxidative chlorination of aromatic sulfides.⁶⁴⁴



Thiophenols can also be converted to sulfochlorides by oxidative chlorination.⁶⁴⁵

Arylsulfonyl chlorides result when aromatic diazonium compounds are made to react with sulfur dioxide in the presence of cupric chloride.⁶⁴⁶



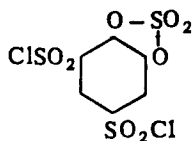
Sulfur dioxide may be employed in solution in glacial acetic acid, formic acid, tetrahydrofuran and alcohol. Reaction proceeds very readily with negatively substituted diazonium chlorides.

Direct Formation of Sulfonyl Chlorides

Many aromatic sulfonyl chlorides may be obtained directly through the reaction of an aromatic compound with chlorosulfonic acid.⁴⁰¹ This method is par-

ticularly useful for the preparation of sulfonyl chlorides derived from phenols and amino compounds. Side reactions may be avoided, and the formation of polysulfonated compounds prevented by carrying out the reaction in a solvent at the lowest possible temperature.⁶⁴⁷

In order to obtain a satisfactory yield a sufficiently large excess of chlorosulfonic acid of high purity must be used. The reaction proceeds with varying ease with different aromatic compounds. *p*-Chloro- and *p*-bromobenzene react at -5 to -15° ; benzene and octylbenzene react readily at ordinary temperature, while nitroaromatic compounds require heating at 100 – 130° .⁶⁴⁸ Hydroxy- and aminosulfonyl chlorides may be obtained from phenols and amines by reaction with chlorosulfonic acid. Phenol and its simplest derivatives readily give disulfonyl chlorides at room temperature, and trisulfonyl chlorides at higher temperatures.⁶⁴⁹ Phenolmonosulfonyl chlorides may be prepared from the carbonic esters of phenols.⁶⁵⁰ *Pyrocatechin* gives a disulfonyl chloride at 110° , together with pyrocatechindisulfonyl chloride sulfuric ester,



The latter is formed in good yield at 150° . Resorcinol gives the 2,4-disulfonic acid, while hydroquinone fails to give a sulfonyl chloride. A mono sulfonyl chloride may be obtained by first converting the phenol to its carboxylic ester.⁴⁰² Alkylaryl esters of phenols also yield monosulfonyl chlorides, and a fair yield of monosulfonyl chlorides is also generally obtainable from alkyl ethers of substituted phenols.⁴⁰³ With piperonylnitrile (3,4-methylenedioxybenzonitrile) condensation to an anthraquinone diimide occurs on treatment with chlorosulfonic acid.⁴⁰⁴ *Acetanilide* and *substituted anilides* are converted to monosulfonyl chlorides.⁴⁰⁵ The method is employed technically in the preparation of saccharin. Other types of compounds yield sulfonyl chlorides with chlorosulfonic acid. Toluenesulfonyl chloride, for example, has been obtained by the action of four parts of chlorosulfonic acid on one of toluene;⁴⁰⁶ *para*-toluenesulfonyl chloride is formed in 70% yield, together with 30% of the *ortho* isomer when the reaction is carried out at 0° – 5° ; a larger proportion of the *para* isomer is formed at higher temperatures. A mixture of hydrogen chloride and fuming sulfuric acid may be employed, in these reactions, instead of chlorosulfonic acid.⁴⁰⁷

Sulfonyl chloride, SO_2Cl_2 , reacting with benzene or toluene in the presence of aluminum chloride, gives sulfonyl chlorides, sulfones also forming as a by-product of the reaction.⁴⁰⁸

Other Sulfonyl Halides

Sulfonyl bromides are formed in varying yield through the reaction of phosphorus pentabromide, PBr_5 , with an alkali sulfonate.⁴¹⁰ An excess of the penta-

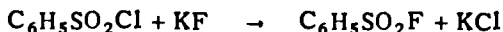
bromide converts the sulfonate into a disulfide.⁴¹¹ Sulfonyl bromides have been prepared also by the action of bromine water on alkali metal sulfonates,⁴⁰⁹ and by oxidizing thiols with bromine in solution in acetic acid or in water.⁴¹²

Sulfonyl iodides result through the reaction of iodine with alkali sulfonates.⁴¹³

Sulfonyl fluorides result through the reaction of fluorosulfonic acid with aromatic compounds:⁴¹⁴



Sulfonyl fluorides result also on boiling under reflux a mixture of sulfonyl chloride with an aqueous solution of potassium fluoride:⁴¹⁵



The yield, with monosulfonyl chlorides, is mostly between 60 to 80%, but is lower with di- and trisulfonyl chlorides. This method has failed only when ortho substituents were present in the aromatic body to induce side reactions.

Sulfonyl fluorides may be prepared by the action of hydrogen fluoride and sodium nitrite on sulfonamides.⁶⁵¹

Properties of Sulfonyl Chlorides

Sulfonyl chlorides are, in general, relatively stable toward water, and many can be steam distilled without decomposition.

The sulfonyl chloride group in aromatic compounds may be replaced with chlorine by treatment with phosphorus pentachloride:⁴¹⁶



The reaction proceeds at 200–220° with compounds of the benzene series, and at somewhat lower temperature with compounds of the naphthalene series. Replacement of the sulfonyl chloride group with chlorine takes place with some compounds by simply subjecting them to the action of the halogen. Phosphorus tribromide converts arylsulfonyl chlorides to disulfides.⁵⁷⁴

Sulfonyl chlorides are converted to sulfonic acids with concentrated sulfuric acid or oleum.⁶⁵² Arylsulfonyl chlorides may be hydrolyzed by heating with water; in many cases hydrolysis proceed only on heating under pressure. Aqueous or alcoholic caustic readily convert arylsulfonyl chlorides to aryl sulfonates.

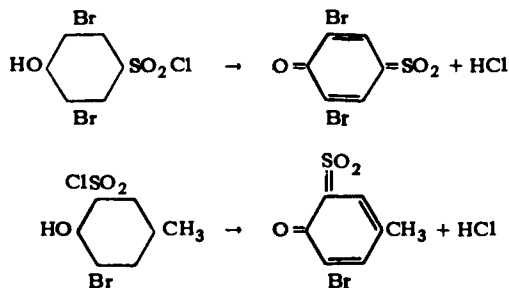
Sulfonyl chlorides are capable of reacting with alcohols or phenols to form sulfonic esters. Polynitrophenols exchange the hydroxyl group for chlorine on reaction with sulfonyl chlorides. Thiosulfonic esters are formed with mercaptans; sodium sulfonates may form with an excess of mercaptan.⁶⁵³

Sulfonyl chlorides react with *amines* to form sulfonamides. The reaction proceeds less vigorously than with the corresponding carboxylic chlorides. Quaternary ammonium compounds are formed through the reaction of arylsulfonyl chlorides with *tertiary amines* such as pyridine, lutidine, and hydroxyquinoline.⁶⁵⁴ With *hydrazines*, mono- and di-arylsulfonylhydrazines are formed, depending on the substituents in the aryl group of the sulfonyl chloride, and the reaction conditions. Arylsulphydroxamic acids are formed with *hydroxylamine*.

Mild reducing agents convert aromatic sulfonyl chlorides to sulfinic acids or thiosulfonic esters.⁶⁵⁵ Energetic reduction results in the formation of thiophenols or disulfides.⁶⁵⁶

Heated with thionyl chloride at 200°, *p*-toluenesulfonyl chloride is converted to *p*-chlorobenzal chloride; at 240°, *p*-chlorobenzoyl chloride is formed. Similarly, *o*-toluenesulfonyl chloride gives, at 240–250°, *o*-chlorobenzoyl chloride.⁴¹⁷

Certain phenol sulfonyl chlorides in which the hydroxy and sulfonyl groups are ortho or para to one another are converted to sulfoquinones on treatment, in acetone solution, with sodium carbonate. Sulfoquinones are obtained in this manner, for example, from 3-bromo-1,2-cresol-5-sulfochloride and 5-bromo-1,4-cresol-3-sulfochloride:⁴¹⁸

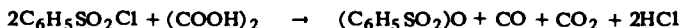


The halogen in sulfonyl fluorides is much less reactive than that in sulfonyl chlorides. In compounds in which both a fluorosulfonyl and chlorosulfonyl group are present, it is therefore possible to replace the halogen by different groups. Benzenesulfonyl fluoride fails to react with ethanol at 100° in the course of several days, although reaction proceeds readily below 15° when alkali is added.

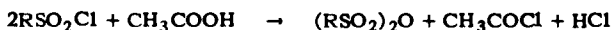
Sulfonic Anhydrides

Arylsulfonic anhydrides are formed through the reaction of arylsulfonic acids or their alkali metal salts with thionyl chloride. Under certain conditions, arylsulfonyl chlorides may also form simultaneously in this reaction. Arylsulfonic anhydrides may be prepared by the action of phosphorus pentoxide on the acids in the presence of an inert carrier.⁶⁵⁷ Sulfonic anhydrides result through the reaction of sulfonic chlorides with silver salts of sulfonic acids. Sulfonic anhydrides are also formed by the reaction of sulfonic chlorides with silver cyanate, or through the reaction of thionyl chloride with sulfonic acids or their salts.⁴¹⁹

Benzenesulfonic chloride reacts with oxalic acid with the formation of benzenesulfonic anhydride:⁶⁵⁸



The reaction of *p*-toluenesulfonyl chloride with glacial acetic acid in the presence of catalytic amounts of sodium chloride results in the formation of *p*-toluenesulfonic anhydride:⁶⁵⁹



Aromatic Sulfonamides

Amides of sulfonic acids are formed by the reaction of sulfonyl chlorides with ammonia or amines:⁴²⁰



The reaction may be carried out simply by warming the sulfonyl chloride with

two equivalents of the amine. The sulfonamide may generally be separated from the amine hydrochloride by extracting the latter with water. The reaction is often carried out in an inert solvent in the presence of sodium carbonate, which serves to eliminate the hydrogen chloride formed in the reaction:⁴²¹



The reaction has been carried out by simply melting a mixture of the amine and sulfochloride and adding potassium carbonate or copper bronze.⁵⁷⁵ Pyridine or alcoholic sodium acetate may be employed instead of sodium carbonate to eliminate the hydrogen chloride formed.⁴²²

In carrying out the reaction in pyridine, all moisture must be eliminated from the reaction mixture, since even as little as 1% moisture can reduce the yield to a fraction of the expected amount. The reaction is usually carried out at 0° in four to five parts pyridine; the temperature is raised to 40° with the less reactive amines. The reaction with *o*-dianisidine requires heating at 100° for 12 hours.⁶⁶⁰ If the sulfonamide does not immediately separate out on pouring in water, the product is stirred with 5% hydrochloric acid for 4 hours, and the precipitate filtered. Several heterocyclic amines fail to react with certain sulfochlorides in pyridine solution. For example, 2-amino-5-phenylmercaptopyrimidine fails to react with *p*-nitro and *p*-acetyaminobenzenesulfochloride.⁶⁶¹ Certain other amines, such as nitroamines give secondary sulfonamides even with one molecular equivalent of the sulfochloride.⁶⁶²

It should be noted that if the reaction in pyridine is carried out at too high a temperature, the sulfochloride may cause the cleavage of the pyridine ring. Cleavage of the pyridine ring may occur at lower temperatures as a side reaction that may be appreciable at times. Pyridine may be replaced with tertiary aliphatic or aliphatic-aromatic amines.⁶⁶³ Excellent results have often been obtained by use of trimethylamine as the acid-binding agent.

The reaction of sulfonyl chlorides with ammonia may be carried out in aqueous medium at 30 to 60°. The reaction mixture is stirred until the odor of sulfonyl chloride disappears; the precipitated sulfonamide is filtered and dissolved in 2*N* sodium hydroxide by warming. The solution is decolorized with carbon, filtered, and the sulfonamide is precipitated by acidifying with hydrochloric acid or carbon dioxide. When hydrogen chloride is employed, care is taken not to make the solution acid to Congo Red in order to prevent the precipitation of any sulfonic acid that may have formed in the reaction. The sulfonamide may be purified by crystallization from water, alcohol, or aqueous alcohol.⁶⁶⁴

Secondary sulfonamides are formed when an excess of sulfochloride is used. The reaction may be carried out with anhydrous ammonia in an inert solvent if the sulfochloride is sensitive to water. The reaction should be carried out at the lowest possible temperature with highly alkali-sensitive compounds, and the reaction mixture should be neutralized immediately after the completion of the reaction.⁶⁶⁵

Sulfonamides have been prepared through the reaction of sulfonyl chlorides with anhydrous liquid ammonia,⁶⁶⁶ and with ammonium carbonate.

Many of the primary aromatic amines with negative substituents and heterocyclic amines give with benzenesulfonyl chloride in the presence of sodium hydroxide, both the mono- and dibenzenesulfonamides, $\text{C}_6\text{H}_5\text{SO}_2\text{NHR}$ and $(\text{C}_6\text{H}_5\text{SO}_2)_2\text{NR}$.⁵⁷⁶ The latter give the monobenzenesulfonamide when heated with alcoholic sodium ethoxide.⁵⁷⁷ The procedure is to mix the base with four molal proportions of 12% potassium hydroxide, and to add 1.5 molal proportion

of the sulfochloride in small portions and with shaking. The mixture is heated toward the end in order to destroy the unreacted sulfochloride, the sulfonate is precipitated by the addition of acid, and filtered or extracted with ether. The *p*-toluenesulfonamides of aniline, β -naphthylamine, and *p*-aminobiphenyl do not react with a second molecule of the sulfonyl halide, while nitroanilines yield the disulfonyl derivatives when treated with an excess of the sulfonyl chloride in the presence of pyridine.⁴²³ The formation of disulfonamides may be avoided by carrying out the reaction in a slightly acid, weakly alkaline, or neutral solution.

Monosulfondiamides may be prepared by the reaction of the sulfonyl chloride with the monoacyl derivative, and subsequent hydrolysis or, they may be prepared by reducing the nitro group in nitrosulfonyl amides.

N-Sulfonylamidophenols may be prepared by the action of a molecular equivalent of the sulfonyl chloride on two of the aminophenol,⁶⁶⁷ or by the reaction of equimolecular quantities of sulfonyl chloride and aminophenol in the presence of dilute caustic or sodium acetate, or in pyridine solution.⁶⁶⁸

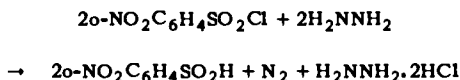
The following is a satisfactory procedure: A tenth molal fraction of the aminophenol, its hydrochloride, or sulfate is dissolved or suspended in 40 cc pure pyridine and a solution of 0.1 mole benzenesulfonyl chloride in 6 to 7 cc pyridine is added with cooling and stirring. After 24 hours the mass is poured into a large volume of ice water containing sufficient hydrochloric acid to combine with all the pyridine, and the mixture is allowed to stand 12 hours. The precipitate is then filtered, washed and dissolved in 5% caustic. The solution is decolorized, made acid to litmus by the addition of hydrochloric acid, and the precipitated product is purified by crystallization from ethyl acetate or from a mixture of benzene and chloroform.

If N-sulfonation fails to proceed in satisfactory manner, the O-sulfonic ester of the sulfonamide is prepared and then partially hydrolyzed.⁶⁶⁹

Cyanamide reacts with sulfochlorides with the formation of N-sulfonylcyanamides.⁶⁷⁰ Dicyandiamide gives N-cyano-N'-arylsulfonylguanidines with sulfochlorides.⁶⁷¹ Guanidine carbonate reacting with sulfochlorides in water or acetone in the presence of potassium carbonate or pyridine gives arylsulfonylguanidines.⁶⁷²

Ethyleneimines react with sulfonyl chlorides in the presence of aqueous alkali, forming N-sulfonylethyleneimines,⁶⁷³ while in the absence of alkalies β -chlorosulfonamides are formed which are converted to sulfonylethyleneimines on warming with alkalies.⁶⁷⁴

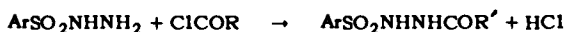
Hydrazine, reacting with sulfonyl chlorides, generally yields the sulfonylhydrazides, $\text{RSO}_2\text{NHNH}_2$, or disulfonylhydrazides, $\text{RSO}_2\text{NHNHSO}_2\text{R}$, depending on the proportion of the chloride and hydrazine.⁵⁷⁸ The general procedure is as follows: A solution of 10 gm arylsulfonyl chloride in 70 cc benzene is added dropwise into a 50% aqueous solution of 2.5 molal proportion of hydrazine with stirring, and agitation is continued for 30 minutes while the liquid is heated to 40 to 50°. After allowing to stand at 0° for a short time, the solid is filtered, washed with water and crystallized from alcohol. Yields range 15 to 100%.⁶⁷⁵ Sulfonyl chlorides in which nitro groups are present in ortho or para position to the sulfonic group, reacting with hydrazine in a mixture of alcohol and benzene at 35–40°, are converted to sulfinic acids:⁴²⁴



The sulfinic acids are formed in 80–90% yield.

Sulfonylhydrazides may be obtained through the reduction of diazonium salts with sulfur dioxide in dilute sulfuric acid or, preferably, in acetic acid.⁶⁷⁶ The method is particularly well adapted for the preparation of nitro substituted sulfonylhydrazides.

Acyl halides react with the primary amino group in sulfonylhydrazides:



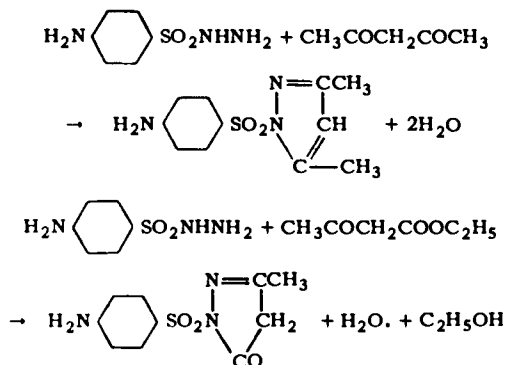
The resulting compounds decompose when heated at 160° in ethylene glycol in the presence of sodium carbonate, giving aldehydes (*McFadyen-Stevens reaction*).⁴²⁵

Arylsulfonylhydrazides decompose on heating to aryl disulfides or aryl thiol sulfones and nitrogen. They yield azides with sodium nitrite.⁶⁷⁷ N-Alkylsulfonylhydrazides may be hydrolyzed to sulfinic acids and a hydrocarbon:



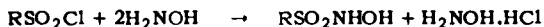
This reaction makes possible the replacement of a halogen in an alkyl halide with hydrogen.⁶⁷⁸

The reaction of sulfonylhydrazides with methylisocyanate gives a thiosemicarbazide.⁶⁷⁹ Pyrazole derivatives are formed with acetylacetone, acetoacetic ester and other carbonyl compounds with active α -methylene:



Benzenesulfonylhydrazones are formed with aldehydes and ketones.⁶⁸⁰

Sulfonyl chlorides react rapidly with hydroxylamine in alcoholic solution to form sulfonyloxamides;⁴²⁶

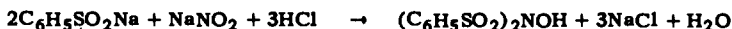


The benzyl ether of hydroxylamine reacts in the same manner.⁴²⁷

Sulfanilhydroxamide, $\text{H}_2\text{NC}_6\text{H}_4\text{SO}_2\text{NHOH}$, reacting with benzoyl chloride in the presence of sodium carbonate or pyridine gives N-benzoylsulfanilamide,



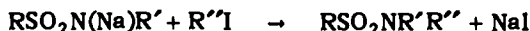
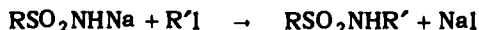
On the other hand, benzenesulfonylhydroxamide, $\text{C}_6\text{H}_5\text{SO}_2\text{NHOH}$, gives with acetic anhydride the N,O-diacetyl derivative, $\text{C}_6\text{H}_5\text{SO}_2\text{N}(\text{OCOCH}_3)\text{COCH}_3$.⁴²⁹ A disulfonylhydroxylamine is formed when an acid is added to an aqueous solution of a sulfinic acid salt and sodium nitrite;⁴³⁰



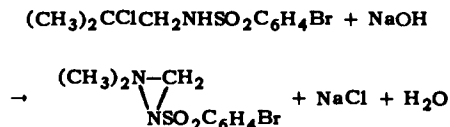
The disulfonhydroxylamine gives with alkali a sodium sulfinat and sodium nitrite,⁴³¹ while with acid the products are sulfonic acid and hydroxylamine. Treatment with nitrous oxide, nitrous acid, or sulfonyl chloride gives a trisulfonylamine oxide. The latter is obtained directly from a sulfinic acid by treatment with fuming nitric acid or nitrogen tetroxide.⁴³² Trisulfonylamine oxides yield salts of sulfinic acids and nitric acid when treated with alkalies, while treatment with acids results in the formation of sulfinic acids and hydroxylamine.⁴³³

Acetanilide-*p*-sulfonyl chloride forms the starting point for the preparation of amino aryl sulfonamides. This compound reacts with amines without loss of the acetyl group, which may be removed subsequently by acid hydrolysis. Monosulfonamides of aromatic diamines are usually prepared by the reduction of nitro or azosulfonamides.⁴³⁴

N-Alkylated sulfonamides may be prepared by the action of alkyl halides, sulfates, or sulfonates upon the amides in aqueous or alcoholic alkaline solution:⁴³⁵



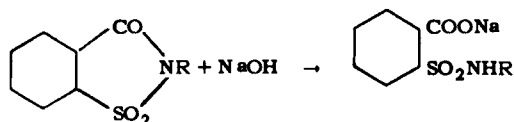
The sulfonamide derived from 2-chloro-2-methylpropylamine, treated with alkalies, gives an ethyleneimine derivative:



Similar reactions resulting in ring closure have been reported with compounds obtained by the addition of *N*-halosulfonamides to olefins.

Tetramethylene bromide reacts with *p*-toluenesulfonamide to form pyrrolidine sulfonamide in 80% yield.⁴³⁶ Since the latter may be hydrolyzed to pyrrolidine, the reaction may serve for the preparation of this base. Sulfonamides of *o*-phenylenediamine, 2,2'-diaminodiphenyl and 4,4'-diaminodibenzyl react with certain α,ω -dihalo compounds to form cyclic compounds.⁵⁷⁹

N-Alkylsaccharins have served as the starting point for the preparation of several alkyl sulfonamides. Reaction with alcoholic caustic results in the formation of *o*-carboxybenzenesulfonamides:⁴³⁷



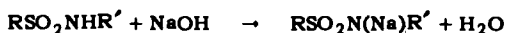
Sulfonamides react with certain carbinols to form *N*-substituted sulfonamides.

Sulfonamides may be acylated without difficulty, the primary sulfonamides yielding mono or diacyl derivatives.⁶⁸¹ Bis-sulfonyl ureas are formed with phosgene,⁶⁸² though arylsulfoisocyanates, RSO_2NCO , may be prepared in high boiling solvents.⁶⁸³ Tri-chlorophosphazosulfonaryls, $\text{RSO}_2\text{N}=\text{PCl}_3$, are formed with phosphorus pentachloride.⁶⁸⁴ *N*-Thiotrichloromethyl-*N*-phenylsulfonamides are obtained with perchloromethylmercaptan

in alkaline solution.⁶⁸⁵ Acylation with phthalyl chloride is employed as a method for the determination of sulfonamides.⁶⁸⁶

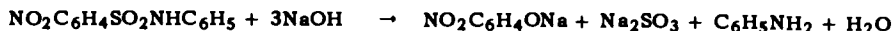
Sulfonamides generally show an acid character, though they are weaker acids than phenol. N-Acylamino derivatives are weaker acids, while N-nitro derivatives show a stronger acid character. The acidity of heterocyclic sulfonamides increases in the order pyrimidine, pyridine, thiazole, thiadiazole.

Benzenesulfonamides derived from a number of primary amines give with sodium hydroxide water-soluble sodium derivatives;⁴³⁸

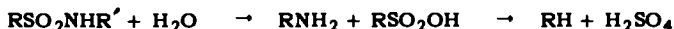


Monosulfonamides of some amines, including those of higher alkylamines and certain hydrogenated cyclic bases, as well as sulfonamides derived from benzylamine, *o* and *p*-toluenebenzylamines, and β -phenylethylamine, are insoluble in aqueous caustic. A number of *p*-bromobenzenesulfonamides derived from aromatic amines are also nearly insoluble in aqueous alkalis. On the other hand, nitrobenzenesulfonamides of aromatic and aliphatic amines, except those obtained from *m*-nitrobenzenesulfonyl chloride and *p*-bromophenylamide, give water-soluble sodium compounds. *p*-Toluenesulfonamide dissolves in boiling sodium carbonate solution. Some sulfonamides of primary amines, including monobenzenesulfonyl derivatives of β -phenylethylamine, *n*-heptylamine, 2-aminodecan and amines of the series $\text{C}_6\text{H}_5(\text{CH}_2)_n\text{NH}-$, $n=1-4$, while insoluble in aqueous sodium hydroxide, dissolve in aqueous alcoholic caustic. Sulfonamides do not dissolve in aqueous ammonia.

Sulfonamides are not hydrolyzed with hot strong aqueous alkalis, unless a nitro group is present in the aromatic ring bearing the sulfonic group in ortho or para position to the latter, in which case hydrolysis results in the severance of the sulfur to carbon bond;⁴³⁹



Hydrolysis with acids results in the formation of amines;⁶⁸⁷



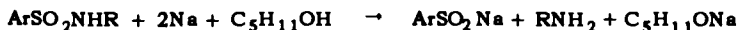
N-Substituted sulfonamides may be hydrolyzed by heating with hydrochloric acid at 120 - 180° in a sealed tube; hydrolysis often takes place at moderate temperatures with sulfonic acid.

Cleavage of the amino group and reduction of the sulfonic group to a thio group takes place on heating sulfonamides with hydriodic acid;⁴⁴⁰

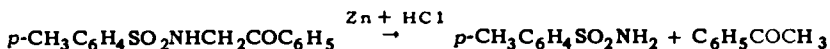


Fusion with alkalis converts N-alkylsulfonamides to an imino compound and a sulfinic acid.⁶⁸⁸

Treatment of sulfonamides with sodium and butyl or amyl alcohol also brings about cleavage of the amine with the formation of a sodium sulfinate;⁴⁴¹

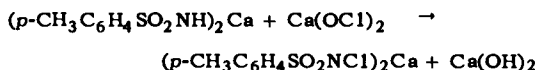


The reaction may be carried out also by use of sodium and liquid ammonia.⁴⁴² A cleavage of this type has been effected with zinc and hydrochloric acid in one case,⁴⁴³ though in other instances, reduction by this method has caused cleavage at the carbon to nitrogen bond:



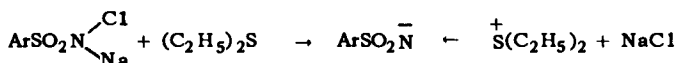
Lithium aluminum hydride or Grignard reagents in xylene convert sulfonamides to amines and sulfinic acids or thiophenols.⁵⁸⁰

Halogens give *N*-halosulfonamides by reaction with an aromatic sulfonamide in neutral or slightly acid solution. Both hydrogens of sulfonamides, RSO_2NH_2 , are thus replaceable with halogen.⁴⁴⁴ *N*-Chlorosulfonamides may be prepared by adding the sulfonamide to a solution of bleaching powder, and acidifying the mixture with acetic acid.⁴⁴⁵ *N*-Chloro-*p*-toluenesulfonamide (Chloramine T) is obtained in the form of its calcium salt by the action of chloride of lime on the calcium salt of *p*-toluenesulfonamide:⁴⁴⁶

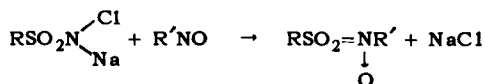


The calcium compound may be converted to the sodium derivative by the action of sodium chloride or sodium acetate. The sodium compound may be readily obtained in the crystalline form. On treating the sulfonamide with a 1.2-equivalent of sodium hypochlorite in aqueous solution, then adding a saturated aqueous solution of sodium chloride, the sodium derivative is obtained as a crystalline precipitate in 90% yield.⁴⁴⁷ The *N*-chloro-*p*-toluenesulfonamide is formed on acidifying the aqueous solution of the alkali metal salt of *N*-chloro-*p*-toluenesulfonamide. Sulfonmonochloroamides have been obtained pure only in the form of their alkali metal salts. The commercial product known as Halazone is a mixture of the mono- and dichloroamides derived from *p*-carboxybenzenesulfonamide.⁴⁴⁸

Chloramine T reacts with thioethers to give sulfinimines:⁵⁸²



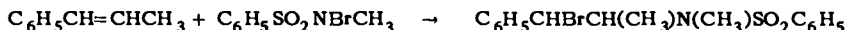
Tribromophosphazosulfonaryls, $\text{ArSO}_2\text{N}=\text{PBr}_3$, are formed in good yield with phosphorus tribromide; *tert*-phosphines in absolute alcoholic solution yield phosphineimines, $\text{RSO}_2\text{N}=\text{PR}_3$.⁴⁵³ Nitroso compounds in pyridine solution give azoxysulfones with Chloramine T:⁶⁸⁹



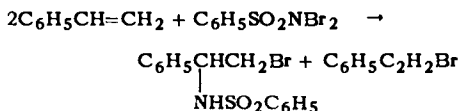
The reaction proceeds at ordinary temperature with some nitroso compounds; with others heating at 80° for several hours may be necessary.

Potassium *p*-toluenesulfonbromoamide precipitates out when a mixture of 1 part by weight of *p*-toluenesulfonamide in solution in 4 parts of water and 1.3 parts of bromine is treated with 2 parts of 50% sodium hydroxide solution.⁴⁴⁹ The sulfondibromoamides are obtained in quantitative yield by shaking the sulfonamides with hypobromous acid.⁴⁵⁰ Hypobromous acid is obtained by the reaction of bromine with mercuric oxide in aqueous suspension.

N-Halosulfonamides react additively with olefins. In the reaction of *N*-halo-*N*-alkyl-sulfonamides with aryl substituted ethylenes, the halogen attaches itself to the carbon atom adjacent to the aromatic group:



On the other hand, in the reaction of sulfondibromides with such olefins, the amido group attaches itself to the carbon atom adjacent to the aromatic group:⁴⁵¹

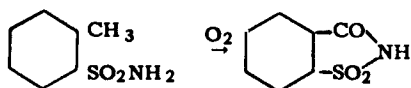


Nitric acid, reacting with benzenesulfonamide or its N-alkylated derivatives, gives an N-nitro compound. An excess of nitric acid brings about the nitration of the benzene ring.⁴⁵²

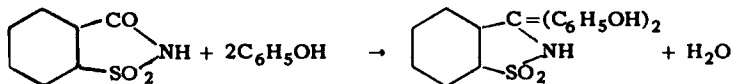
Arylsulfonamides are converted to sulfonic acids by treatment with sodium nitrite and concentrated sulfuric acid of low water content.⁵⁸¹ N-Alkylated and acylated sulfonamides give nitroso derivatives by this treatment.

Sulfonamides and N-alkylsulfonamides react with formaldehyde to form N-methyl derivatives.⁶⁹⁰ Other aldehydes act in a similar manner.⁶⁹¹ Sulfonylimines, $RR'S=NSO_2R$, are formed when sulfonamides react with sulfoxides in the presence of acetic anhydride or phosphorus pentoxide.⁶⁹² The amino group in primary and secondary aromatic sulfonamides undergoes the normal reactions of amines with cyanic and isocyanic acids resulting in the formation of N-sulfonylureas.⁶⁹³

The o-sulfonamide derived from benzoic acid apparently cannot exist in the free state but is known in the form of its internal imide, *saccharin*. This compound is obtained by the oxidation of o-toluenesulfonamide:⁴⁵⁴

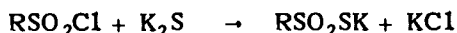


o-Toluenesulfonic acid is obtained in a maximum yield of 60% through the sulfonation of toluene under carefully controlled conditions. It may be isolated from its mixture with the p-isomer by precipitating the latter as its barium salt.⁴⁵⁵ Phenols condense with saccharin in the presence of sulfuric acid to form sulfamphthaleins, compounds resembling phthaleins:⁴⁵⁶



Thiosulfonic Acids

Thiosulfonic acids, RSO_2SH or $RSOS.OH$, are obtained in the form of their salts from sulfonic chlorides and potassium sulfide:⁴⁵⁷



A sulfinic salt apparently is formed first with separation of sulfur and subsequent combination of the sulfur and sulfinic salt.

Reduction of Sulfonic Acids or their Derivatives

Sulfonic acids, their esters and salts resist reduction, but sulfonyl chlorides and sulfonamides may be reduced successfully. Sulfinic acids are formed when reduction is effected under mild conditions. Sulfinates are obtained, for example, when sulfonyl chlorides are reduced with zinc dust in alcoholic or ethereal solution:



Reduction of sulfonyl chlorides in ethereal solution with sodium also leads to the formation of sulfinates.⁴⁵⁸ Reduction under drastic conditions, such as by use of zinc and hydrochloric acid or sulfuric acid results in the formation of thiophenols.⁴⁵⁹ Tin or stannous chloride and hydrochloric acid have also been

employed frequently for the purpose.⁴⁶⁰ If a nitro group is present in the molecule of the sulfonyl chloride, it is reduced to an amino group.⁴⁶¹ Sulfonyl fluorides are reduced with difficulty.

Aryl sulfonamides are reduced when treated with concentrated aqueous hydriodic acid, especially in the presence of phosphonium iodide, giving thiophenols:



Replacement of Sulfonic Groups with other Groups or Elements

The sulfonic group in aromatic sulfonic acids may be replaced with *hydrogen* by heating with aqueous sulfuric acid.

The procedure is to mix the sulfonic acid with about five times its weight of 70% sulfuric acid, to heat the mixture between 140° and 190° and to pass superheated steam through the liquid. The desulfonated body distills over, if it is volatile with steam; otherwise it is recovered from the acid solution. This method is of wide applicability.⁴⁶² Hydrogenated naphthalenesulfonic acids, subjected to this treatment yield the hydrocarbon, together with a disulfonated product.

Ease of hydrolysis varies within wide limits; thus, while hydrolysis is occasionally possible at an elevated temperature under pressure, the reactions of 2-naphthylamine- and 2-naphthol- 1-sulfonic acid with water proceed at a little above 0°. Hydrolysis of sulfonic acids may be catalyzed with mercury sulfate, or aluminum hydroxide.⁵⁷² The sulfonic group in 1-naphthalene sulfonic acid is hydrolyzed at 149-155° with dilute sulfuric acid, while the 2-sulfonic group is not affected under these conditions.⁵⁷³

Replacement of the sulfonic group with hydrogen may be brought about also by heating with concentrated hydrochloric acid in a sealed tube or autoclave at 150-200°. Many sulfonic acids resist this treatment, however, even at temperatures as high as 250°. ⁴⁶³

Removal of the sulfonic group and its replacement with hydrogen is accomplished also by distilling the free sulfonic acid or, preferably, its ammonium salt or a mixture of its lead salt with ammonium chloride.⁴⁶⁴ A sulfone is formed as a by-product in this reaction.

The presence of a methyl group in *ortho* or *para* position to the sulfonic group facilitates hydrolysis, but a methyl group in *meta* position has little effect.

Meaitylenesulfonic acid is almost completely hydrolyzed by 38% hydrochloric acid in 15 minutes at 80°. *2,4,6-Triethylbenzenesulfonic acid* decomposes to triethylbenzene when heated alone or even when crystallized from alcohol.

Di-, tri- and tetrabromobenzenesulfonic acids are hydrolyzed only when heated with concentrated hydrochloric acid at 150 to 250°. *2,3-Dinitro-2,4,6-tribromobenzenesulfonic acid* is hydrolyzed when heated with water at 230°.

Phenolsulfonic acids undergo hydrolysis readily when the hydroxyl group is in *ortho* or *para* position to the sulfonic group.⁵⁴³ *2-Halophenolsulfonic acids* are readily hydrolyzed to *ortho* halophenols.⁵⁴⁴

Naphthalene- α -sulfonic acid is hydrolyzed with steam at 160° to naphthalene, while the *β -sulfonic acid* is unaffected by this treatment. This fact is utilized in the commercial production of pure *β -naphthol*.

β-Naphthol-*α*-sulfonic acid is hydrolyzed more readily than phenolsulfonic acids. Naphthionic acid is rapidly converted to *α*-naphthylamine when heated at 180° with sulfuric acid diluted with half its volume of water. The 1-amino-4,6,8-trisulfonic acid gives naphthol-6,8-disulfonic acid with loss of ammonia when heated with water. 2,3-Dihydroxynaphthalene is formed when 3-amino-2-naphthol-7-sulfonic acid is heated at 180 to 200° in acid solution. 1,8-Dichloronaphthalene-3-sulfonic acid is resistant to hydrolysis.

Hydroxyanthraquinonesulfonic acids in which the hydroxyl group is *ortho* or *para* to the sulfonic group are hydrolyzed readily.⁵⁴⁵ 8-Nitroanthraquinone-1-sulfonic acid, heated at 190 to 200° with 50% sulfuric acid in the presence of a mercury salt is converted to nitroanthraquinone.

1,2-Anthraquinone-4-sulfonic acid gives 4-methoxy-1,2-anthraquinone in 85% yield when heated with methyl alcoholic sulfuric acid.⁵⁴⁶

Octahydroanthracenesulfonic acid is hydrolyzed readily when treated with hydrochloric acid. Hydrolysis of octahydrophenanthrenesulfonic acid requires more drastic treatment.

Removal of a sulfonic group and its replacement with a hydrogen atom may be brought about by *reducing agents*.

The sulfonic group in *α*-naphthalenesulfonic acids is readily removed by reduction with sodium amalgam, but the removal of the sulfonic group in *β*-sulfonic acids requires more vigorous treatment.⁵⁴⁷

Anthraquinone-2-sulfonic acid is reduced to anthracenesulfonic acid with sodium amalgam or zinc.⁵⁴⁸ Sodium amalgam is especially suited for the removal of the *α*-sulfonic group from the naphthalene ring. Amalgam of low sodium content, say between 0.1 and 0.5% should be used to avoid reduction of the naphthalene ring. Sulfonated anthraquinonecarboxylic acids are converted to the corresponding anthracene derivatives with zinc and alkali.⁵⁴⁹ Many hydroxy- and aminoanthraquinonesulfonic acids lose the sulfonic group when treated in acid solution with zinc dust, or in alkaline solution with sodium hydrosulfite. An *ortho* or *para* hydroxyl group facilitates the removal of the sulfonic group.⁵⁵⁰

Removal of the sulfonic group and its replacement with hydrogen is accomplished by distilling the free sulfonic acid or, preferably, its ammonium salt, or a mixture of its lead salt with ammonium chloride.⁴⁶⁴ A sulfone is formed as a by-product in this reaction.

The sulfonic group in aromatic sulfonic acids can be replaced with *halogens* only if amino or hydroxyl groups are present in the molecule in *ortho* or *para* position to the sulfonic group, and even when this condition is satisfied, replacement still depends on the presence of other substituents.

2,6-Dibromosulfanilic acid is converted to 2,4,6-tribromoaniline when subjected to the action of bromine. Treatment of the sulfanilic acid with iodine monochloride results in the formation of 4-iodo-2,6-dibromoaniline. 4,6-Dibromoaniline-2-sulfonic acid reacts in a similar manner.⁴⁶⁵ The sulfonic group in certain amino and hydroxynaphthalenesulfonic acids is also replaceable with bromine.⁴⁶⁶ Anthraquinone-*α*- and *β*-sulfonic acids, treated with chlorine in boiling aqueous solution, give the corresponding monochloroanthraquinones. The sulfonic groups in anthraquinonedisulfonic acids are also replaced with chlorine by this treatment. Replacement with chlorine may be brought about also by boiling the anthraquinone sulfonic acids with a mixture of hydrochloric acid and sodium chlorate.⁴⁶⁷

The sulfonic group in many aromatic sulfonic acids may be replaced with the

cyano group by heating with potassium cyanide. The replacement of sulfonic groups by carboxyl groups has been brought about by fusing a mixture of the sulfonic acid with potassium formate.⁴⁶⁸

The sulfonic group in certain aromatic compounds, notably phenol- and naphtholsulfonic acids, may be replaced with a *nitro* group by the action of nitric acid or nitrous gases. *α*-Naphthol-2,4-disulfonic acid gives 2,4-dinitro-*α*-naphthol; *o*-cresol-3- and 4-sulfonic acids give the 3,5-dinitro derivative.

Sulfonic groups activated by nitro groups or other negative groups attached to the aromatic nucleus or replaceable with the *amino* group. 2,4-Dinitrobenzenesulfonic acid gives 2,4-dinitroaniline when heated with ammonia in a sealed tube.⁴⁶⁹ Naphthalene-1,3,5-trisulfonic acid is converted to 1,3-diaminonaphthalene-5-sulfonic acid when heated with ammonia and sodium hydroxide under pressure.⁴⁷⁰ 1-Aminonaphthalene-3,6-disulfonic acid and the corresponding hydroxydisulfonic acids give 1,3-diaminonaphthalene-6-sulfonic acid when heated with ammonia under pressure.⁴⁷¹ Sulfonic groups attached to the anthraquinone nucleus are also replaceable with ammonia by this treatment.⁴⁷² The addition of certain inorganic salts, among them barium chloride, sodium dichromate, and sodium arsenite, facilitate the replacement of the sulfonic group with an amino group.⁴⁷³ Sulfonic groups may also be replaced with the amino group by heating a mixture of the potassium salt of the sulfonic acid with *sodamide*. The reaction proceeds in an unsatisfactory manner with benzenesulfonic acid, but it proceeds more readily with naphthalenemonosulfonic acids.⁴⁷⁴

Thiosulfonic Esters

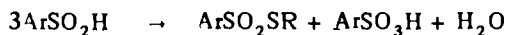
Thiosulfonic esters may be prepared through the oxidation of disulfides with a slight excess of hydrogen peroxide in acetic acid solution.⁶⁹⁴



The procedure may be illustrated by the preparation of the 2-naphthyl ester of naphthalene-2-thiosulfonic acid:⁶⁹⁴ A solution of 5 gm β -naphthyl disulfide in 130 cc warm acetic acid is rapidly cooled, 3.5 gm of perhydrol are added and the mixture is allowed to stand 30 hours with occasional shaking. The solution is filtered and the thiosulfonic ester is precipitated by the addition of water and sodium chloride. The compound is purified by repeated crystallization from alcohol. The yield is 40% of the theoretically expected quantity.

Thiosulfonic esters have been prepared also by oxidizing disulfides with perbenzoic acid.⁶⁹⁵ Tetrahalides obtained by the addition of halogens to disulfides may be converted to thiosulfonic esters by hydrolysis.⁶⁹⁶

Thiosulfonic esters have been prepared by heating sulfonic acids with dehydrating agents such as sulfuric or phosphoric acids:⁶⁹⁷



Such esters have been prepared also by the action of a small amount of hydriodic acid on sulfonic acids in boiling aqueous solution containing an excess of sulfurous acid.⁶⁹⁸

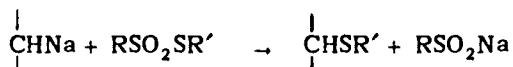
Thiosulfonic esters may be prepared through the reaction of alkali metal

salts of thiosulfonic acids with alkyl halides in alcoholic solution,⁶⁹⁹ and by the reaction of sulfonyl chlorides with silver sulfinates.⁷⁰⁰ The reaction of sulfonic iodides with silver mercaptides gives thiosulfonic esters. This method makes possible the preparation of esters difficultly accessible by other methods.⁷⁰¹ Direct reaction of sulfonic chlorides with mercaptans results in the formation of disulfides and sulfinic acids,⁷⁰² though reaction in benzene solution in the presence of pyridine may give thiosulfonic esters in 20% yield.

Thiosulfonic acids may be oxidized to disulfones with hydrogen peroxide; more vigorous oxidizing agents, such as bromine and potassium permanganate convert them to sulfonic acids.⁷⁰³

Thiosulfonic esters are hydrolyzed to sulfinates and disulfides by dilute alkalis and by baryta water.⁷⁰⁴

Reactive methylene groups may be thioalkylated with thiosulfonic esters:

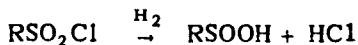


SULFINIC ACIDS

Methods of Preparation

By Reduction of Sulfonyl Halides

Sulfinic acids are generally obtained by reducing sulfonyl halides:



The reducing agents usually employed are *zinc dust* in neutral and basic aqueous or alcoholic media,⁴⁷⁵ *iron* or *zinc* and *acetic acid*,⁴⁷⁶ *stannous chloride* and hydrochloric acid, sodium amalgam in benzene,⁴⁷⁷ and sodium sulfide and alkali metal sulfites in the presence of caustic.⁴⁷⁸ Reduction of benzene sulfonyl chloride to the corresponding sulfinic acid may be effected by adding the calculated quantity of lithium aluminum hydride to the sulfonyl chloride at -65°. ⁵⁵³ Sodium iodide in the presence of zinc dust or sodium sulfate has been employed for the reduction of sulfonyl chlorides to sulfinic acids.⁵⁵⁴

The procedure⁴⁷⁹ generally adopted in carrying out the reduction with *zinc dust* is as follows: The metallic dust is added to seven or eight times its weight of water heated at 70°, the suspension is vigorously agitated and the sulfonyl chloride is added gradually in the course of ten minutes. Usually there is an automatic rise in temperature to about 80°. The mixture is stirred ten minutes longer, and is then heated to 90° and a molecular equivalent of strong caustic is added. The liquid is next made strongly alkaline with sodium carbonate and is filtered. The filtrate is evaporated to small volume and cooled to crystallization. The yield is about 64% of the theoretical. The amount of zinc used for the reduction should be 10% in excess of two atomic equivalents per mole of sulfonyl chloride to be reduced.

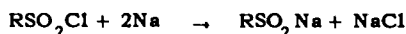
Reduction with *sodium sulfide* is accomplished by adding the sulfonyl chloride to a solution of one and a quarter molecular proportions of sodium sulfide in an equal amount of water, and heating the mixture on a water bath for one hour. The solution is

filtered and cooled to 0°, whereupon the pure sodium sulfinate usually crystallizes out.⁴⁸⁰

Six molecular equivalents of the reducing agent are employed when reduction is carried out with an *alkaline sulfite*. As the reaction proceeds, the liquid tends to become acid; aqueous caustic is added from time to time to keep the solution slightly alkaline. When reduction is complete, the sulfonic acid is precipitated by the addition of hydrochloric acid. The yield varies between 60 and 80%.

This method seldom fails; failure is observed with certain alkali-sensitive sulfochlorides such as 2,4-dinitrobenzene sulfonyl chloride. The method is suitable for the preparation of water-sensitive sulfinic acids, such as 4-acetyl-amino- and *p*-carbo-methoxyaminobenzene sulfinic acids. Nitroarylsulfinic acids, and other sulfinic acids with susceptible substituents can also be prepared successfully by the method.

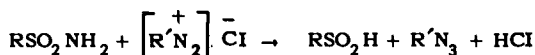
In carrying out the reduction with mercury amalgam, the sulfonyl halide is dissolved in benzene and 4% sodium amalgam is added a little at a time. Slightly more than two atomic equivalents of sodium are employed per mole of sulfonyl halide. The reaction may be expressed as



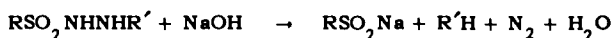
The solid which is deposited should be entirely soluble in water. It is dissolved in the least amount of water and the solution is acidified to obtain the free acid. The yield is nearly theoretical.

Disulfinic acids have been prepared by the reduction of disulfonyl chlorides, but no trisulfinic acid has yet been prepared.

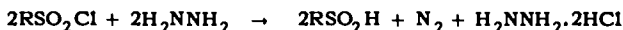
Sulfinic acids are formed in certain reactions involving sulfonamides, sulfonhydrazides, and sulphydroxamic acids. Sulfonamides give sulfinic acids by reaction with diazonium salts in alkaline solution:⁷⁰⁵



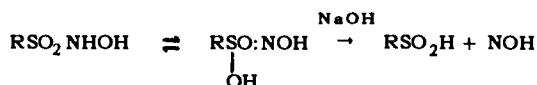
Arylsulfonhydrazides readily decompose to arylsulfonic salts in the presence of alkali:⁷⁰⁶



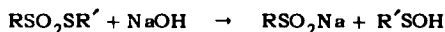
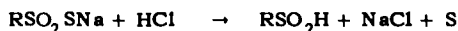
The reaction of arylsulfochlorides with excess hydrazine may lead to the formation of sulfinic acids:



This reaction proceeds with ease with *o*-nitrosulfonyl hydrazides,⁷⁰⁷ but 2,4-dinitrobenzenesulfinic acid cannot be obtained by this method.⁷⁰⁸ Arylsulfoxamic acids decompose under the action of alkalis to arylsulfinic acids and nitroxy:⁷⁰⁹

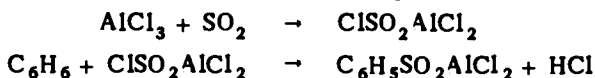


Arylthiosulfonic salts or esters may be hydrolyzed to arylsulfinic acids:⁷¹⁰



Preparation of Sulfinic Acids by Friedel-Crafts Reaction

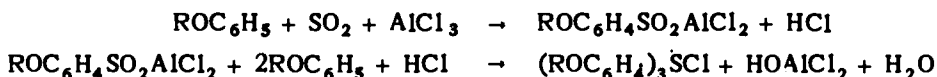
Condensation takes place with the formation of a sulfinic acid when sulfur dioxide is passed through an aromatic hydrocarbon to which a little hydrogen chloride is added and which contains aluminum chloride in suspension.⁴⁸¹ An intermediate aluminum chloride complex is apparently formed first, and reacts with the aromatic body to give the sulfinic compound:⁴⁸²



Good yields are obtained only when the reaction is conducted in the complete absence of moisture, and the final complex is first decomposed with alkalis before treatment with acid.

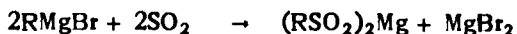
The procedure may be illustrated by the preparation of *benzenesulfinic acid*: Benzene is mixed with half its weight of powdered aluminum chloride, and hydrogen chloride is bubbled through the mixture until about 1.5% of the weight of benzene has been absorbed. A slow current of sulfur dioxide is then passed for five hours through the mixture kept at 0°, with good agitation. The reaction mixture is then allowed to stand for twenty-four hours, effectively protected from atmospheric moisture, after which it is poured onto ice. The resulting solution is made alkaline with caustic, and the excess benzene is removed by distillation with steam. The residual liquid is saturated with carbon dioxide, the precipitated aluminum hydroxide is filtered off, and the filtrate is concentrated by evaporation. The free benzenesulfinic acid precipitates out on the addition of hydrochloric acid.⁴⁸³

Phenol ethers react with sulfur dioxide readily under the action of aluminum chloride even in the absence of hydrochloric acid, forming sulfinic acid complexes. The reaction does not stop at this stage, however, but proceeds farther, and results in the formation of sulfonium compounds:



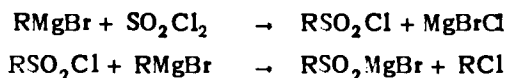
Preparation of Sulfinic Acids by the Grignard Reaction

Halomagnesium compounds of aromatic bodies react with sulfur dioxide to form the magnesium salt of a sulfinic acid:⁴⁸⁴



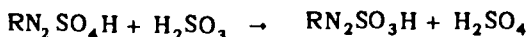
For example, when dry sulfur dioxide is passed into an ethereal solution of phenylmagnesium bromide cooled in a freezing mixture, a white crystalline body separates out which, on crystallization from water, gives the magnesium salt of benzene sulfinic acid. The yields vary between 50 and 60% of theoretical. *o*-Nitrosoarylsulfinic acids cannot be prepared by this method.⁴⁸⁵

Aromatic sulfinic acids may be obtained also through the reaction of aryl magnesium halides with sulfonyl chloride.⁴⁸⁶ The reaction probably proceeds in two stages:



Sulfinic Acids from Diazo Compounds

The diazo group in aromatic diazonium compounds may be replaced with the sulfinic group by the action of sulfur dioxide in the presence of copper.⁴⁸⁷ Copper oxide, cuprous hydroxide or cuprous sulfite may be used in place of copper. A diazonium sulfite is probably first formed, and is subsequently decomposed giving rise to the sulfinic acid:



Copper or copper oxide should be used in stoichiometric quantities. The use of the sulfate of the diazonium compound is generally preferable to that of the chloride, since the use of the latter favors the formation of a little aryl halide.

The diazonium salt is dissolved in an excess of sulfuric acid and sulfur dioxide is conducted through the well-cooled solution until the concentration of the dioxide reaches 5 gm per cc. Copper powder, or other copper catalyst, is now gradually added with cooling as long as nitrogen evolution continues. The passage of sulfur dioxide through the solution is continued and the mixture is well agitated during the introduction of the catalyst. Both the precipitate and the solution are extracted with ether, and the ether extract is shaken with aqueous sodium hydroxide, which dissolves the sulfinic acid. Addition of acid to the caustic solution causes the precipitation of the sulfinic acid. If a heavy precipitate appears during the passage of sulfur dioxide before the addition of copper, too little sulfuric acid has been used, or the passage of sulfur dioxide has been continued too long. Insufficient cooling also causes this difficulty.

In many cases it is preferable to add the solution of the diazo compound to a mixture of the saturated aqueous solution of sulfur dioxide with copper. Diazo compounds derived from naphthylamines are best converted to sulfinic acids by this method.

Replacement of the diazonium group with a sulfinic group may be brought about by the action of an alcoholic solution of sulfurous acid in the presence of a little copper sulfate.⁴⁸⁸ In this reaction diazonium chlorides give better results, on the whole, than the sulfates. Nearly quantitative yields are obtained when sufficient sodium sulfite is added to the diazonium solution to convert the diazo compound to the sulfite, and the free acid to its sodium salt, then adding alcohol and the copper catalyst.

As an example, 9.3 parts of aniline dissolved in 40 parts of 20% hydrochloric acid are diazotized at 0°-5° with a solution of 7 parts of sodium nitrite in 10 parts of water. A mixture of 30 parts of 40% sodium bisulfite and 35% alcoholic sulfurous acid is added to the diazo solution, keeping the temperature at 0-5°. Finally, a concentrated aqueous solution of 2.5 parts of copper sulfate is added, and the mixture is agitated, allowing the temperature to rise to 15-20°. After the evolution of nitrogen ceases, the solution is neutralized with sodium carbonate, the alcohol is distilled off, and the cooled residue is acidified with hydrochloric acid to precipitate the sulfinic acid.

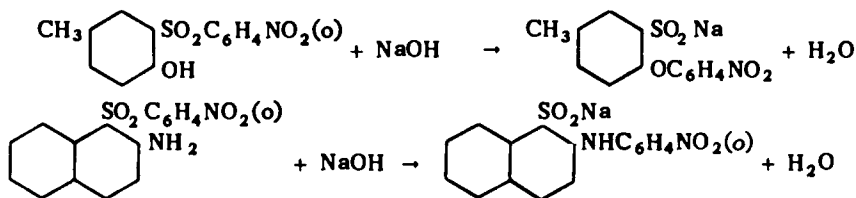
Diazonium salts that are more stable should be subjected to the reaction at a somewhat higher temperature. The reaction should be carried out at 30°, for example, with the diazonium compound derived from anisidine.

Sulfinic Acids from Sulfones

Aromatic sulfinic acids are obtained by heating aromatic sulfones, $\text{RSO}_2\text{R}'$, with alkaline reagents.⁵⁵⁵ Sulfinic acids have been obtained, generally in good

yield, from a large number of symmetrical and unsymmetrical sulfones by heating at 235° with sodium ethoxide.⁴⁸⁹ Cleavage may also be brought about with amines and phenylhydrazine,⁷¹¹ or with alkali metals or alkali metal amides.⁷¹² Aromatic sulfinic acids have been obtained through the cleavage of diaryl disulfones $\text{ArSO}_2\text{SO}_2\text{Ar}$, with piperidine.⁷¹³

Certain aromatic sulfones in which a hydroxyl or an amino group stands in ortho position to the sulfonic group undergo rearrangement to a sulfinic acid when heated with dilute alkali:⁵⁵⁶



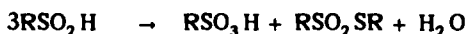
In general, a necessary condition for the occurrence of the rearrangement is the presence of an *ortho* or *para* nitro group, or a sulfonyl substituent in the migrating acyl group.

p-Nitrophenyl-2-hydroxyethylsulfone undergoes rearrangement to *o*-nitrophenoxylethylsulfinic acid:⁴⁹⁰



Character and Behavior of Sulfinic Acids

Aromatic sulfinic acids are more stable than aliphatic sulfinic acids. They tend to undergo decomposition to a sulfonic acid and a disulfide on long standing:



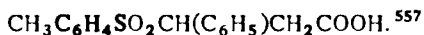
Decomposition is accelerated by dilute acids or on heating with water at 130°. They are slowly oxidized to sulfonic acids when exposed to air. Sulfonic acids are somewhat stronger acids than the corresponding carboxylic acids.

Ferric salts of these acids are insoluble and may be quantitatively precipitated by adding a solution of ferric chloride to their strongly acid aqueous solution. Alkalies convert the ferric salts to alkali sulfinates, from which the acids may be freed by the action of hydrochloric acid.⁴⁹¹

The sulfinic group in aromatic sulfinic acids may be replaced with hydrogen by fusion with caustic:

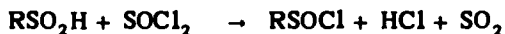


Aryl sulfinic acids are capable of adding to α , β -unsaturated acids to form sulfones, cinnamic acid yielding with toluenesulfinic acid the compound



Sulfinic acids react with aldehydes to form α -hydroxymethylsulfones.⁷¹⁴ *p*-Substituted sulfinic acids, RSO_2H , react additively with azo compounds, $\text{R}'\text{N}=\text{NR}''$, to form the sulfonylhydrazides $\text{RSO}_2\text{NR}'\text{NHR}''$.⁷¹⁵

Sulfinic acids may be converted to their *chlorides* by treatment in ethereal solution with excess thionyl chloride:⁴⁹²



The reaction proceeds vigorously in the beginning, but must be completed by heating on a water bath, after the ether has been evaporated off. The excess thionyl chloride is driven off first by applying vacuum at ordinary temperature, then by heating to 50° under vacuum.

The sodium salts of certain sulfinic acids react readily with sulfuryl chloride to form sulfinic chlorides; but others, among them sodium benzenesulfonate, fail to react even when heated to high temperatures. The free benzenesulfonic acid reacts rapidly to form the sulfinic chloride.⁵⁵¹

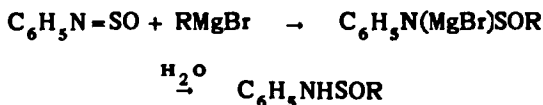
The *anhydrides* of sulfinic acids result when aromatic sulfinic acids are treated with acetic anhydride in the presence of a little concentrated sulfuric acid.⁴⁹³

Esters of sulfinic acids may be obtained by heating alkali metal sulfinates with chlorocarbonic esters:⁴⁹⁴



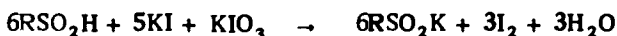
The esters result also through the reaction of sulfinic acids with alcoholic hydrochloric acid. Alkali metal sulfinates reacting with alkyl iodides give mixed sulfones.⁴⁹⁵

Sulfinic *amides* are obtained through the reaction of sulfinic chlorides with ammonia or primary or secondary amines. The reaction should be carried out in an indifferent solvent with great care.⁴⁹⁶ Sulfinic amides are less stable than carboxylic amides. Anilides of sulfinic acids have been obtained by reacting organomagnesium halides with thionylaniline.⁴⁹⁷

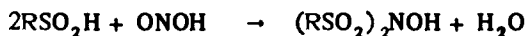


The reaction proceeds well with both alkyl and aryl magnesium halides.

Sulfinic acids may be determined iodometrically.⁷¹⁶ The reaction forming the basis of this determination is as follows:



Arylsulfinic acids give insoluble N,N' -diarylsulfonylhydroxylamines with nitrous acid:⁷¹⁷



This reaction may serve for the gravimetric determination of aromatic sulfinic acids.

Thiosulfinic Esters

Thiosulfinic esters result in almost quantitative yield through the reaction of sulfonyl chlorides with thiols in the presence of pyridine:⁷¹⁸

The *general procedure* is as follows: A solution of 0.02 mole of sulfinic chloride in 20 cc anhydrous ether is added with agitation and cooling, to a mixture of 0.2 mole mercaptan, 30 cc anhydrous ether and 18 gm pyridine, in the course of three minutes. The solution is gently warmed for ten minutes and is then poured into 40 cc of water to which 10 cc of normal sulfuric acid have been added. The ether layer is washed with water, dried with calcium chloride and the ether is removed by distillation under reduced pressure. The residue is washed with petroleum ether, dissolved in benzene or chloroform, and precipitated by the addition of sufficient petroleum ether to produce a turbidity, and cooling to -5 to -10.

Thiosulfinic esters may be prepared through the oxidation of disulfides with peracids.⁷¹⁹ The reaction may be carried out in chloroform. Carbon tetrachloride, ethyl alcohol, ether, acetone, acetaldehyde, acetic acid or acetone may also be used as the reaction medium.

The *general procedure* is to add a solution of 0.1 mole perbenzoic acid in 200 cc chloroform, drop by drop and with agitation, to a solution of 0.1 mole of the disulfide in one liter chloroform cooled in an ice bath. After allowing the mixture to stand at room temperature for 30 to 60 min, it is shaken with 0.1 mole of 5% aqueous sodium bicarbonate, then with a more dilute bicarbonate solution and finally the chloroform layer is withdrawn and washed with water. The washings are extracted with 50 to 100 cc chloroform, the combined chloroform extracts are dried with anhydrous sodium sulfate and subjected to fractional distillation to isolate the ester. The crude ester may be purified by crystallization from ether.

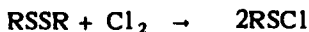
Reaction proceeds to completion within 30 minutes at 25° with normal disulfides; secondary sulfides react with difficulty, while tertiary disulfides fail to yield thiosulfinic esters. Yields vary between 20 and 65% of theory.

Thiosulfinic esters of the aromatic series are more stable than those of the aliphatic series. They show less tendency toward disproportionation into a sulfide and a thiosulfonic ester than methanethiosulfinic methyl ester.

SULFENIC ACIDS⁴⁹⁸

Only one example of a free sulfenic acid, RSOH, is known, namely anthraquinone-1-sulfenic acid.⁴⁹⁹ This compound has been prepared by hydrolyzing the corresponding ester with caustic, and acidifying the resulting solution. Derivatives of numerous aromatic sulfenic acids have been successfully prepared however.

Sulfenyl chlorides, RSCl, are formed by the action of chlorine on disulfides, RSSR:⁵⁰⁰

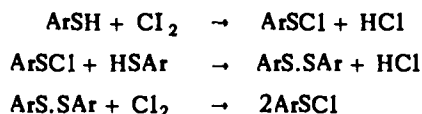


The disulfide is dissolved in an inert solvent, such as carbon tetrachloride, chloroform, or ethyl chloride; the solution is cooled and chlorine is passed through it, keeping the concentration of free chlorine in solution at a low level. The reaction must be

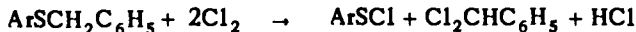
carried out in the absence of light and moisture. Solvents such as benzene, pentane, etc., which are normally attacked by chlorine, can be employed under certain conditions. The yields are nearly quantitative in some cases.

When nitro groups are present in the aromatic nucleus, the tendency toward nuclear substitution of the halogen is greatly reduced, and better yields of the desired sulfenyl chloride are obtained.

Sulfenyl chlorides are also formed by the action of chlorine on thiophenols. The reaction apparently proceeds in three stages:



The thiophenol is added gradually to a well-cooled solution of chlorine in an inert solvent such as chloroform or carbon tetrachloride containing a slight excess of the halogen, and this excess is eliminated immediately upon completion of the reaction by the application of vacuum.⁵⁰¹ Thio- β -naphthol yields 1-chloronaphthalene-2-sulfenic chloride.⁵⁰² *p*, *p'*-Diphenyldimercaptan gives the disulfenylchloride. If the reaction of chlorine with an aromatic mercaptan is carried out in acetic acid solution, sulfonyl chlorides are obtained.⁵⁰³ Sulfenyl chlorides are also obtained by the action of chlorine on aromatic benzyl sulfides; the benzyl group is transformed to benzal chloride in this reaction:



Triphenyl thiocarbonyl, reacting with sulfuryl chloride, gives triphenylmethylsulfenyl chloride:⁵⁰⁴



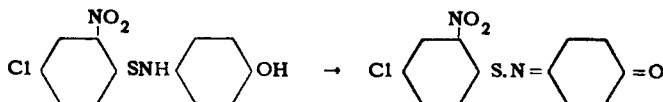
The chlorine in this compound is less mobile than in purely aromatic sulfenic chlorides.

Aromatic sulfenyl bromides may be prepared by the action of bromine on aromatic disulfides or on thiophenols. Sulfenyl bromides are less stable than the chlorides.

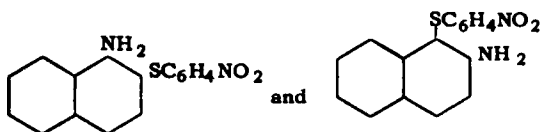
Ammonia, reacting with benzenesulfenic chloride, gives the imide:



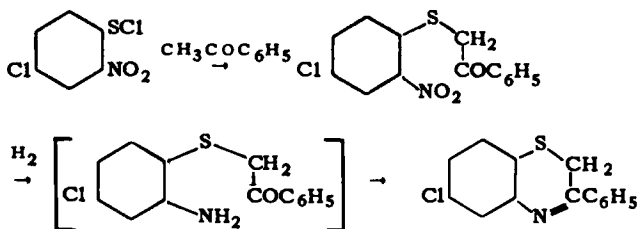
An amide, $\text{NO}_2\text{C}_6\text{H}_4\text{SNH}_2$, has been obtained from *o*-nitrophenylsulfenyl chloride and ammonia; the amide readily changes to the imide with release of ammonia. The methylamide obtained with *o*-nitrophenylsulfonyl chloride and methylamine also changes to the methylimide with separation of methylamine. Sulfenyl chlorides reacting with aniline give anilides, RSNHC_6H_5 . The *p*-hydroxyanilide obtained by the reaction of *p*-hydroxyaniline with 4-chloro-2-nitrophenylsulfenic chloride has been converted to 4-chloro-2-nitrophenylquinonesulfimine by oxidation with bichromate in acetic acid solution:⁵⁰⁵



Naphthylamines reacting with *o*-nitrophenylsulfenyl chloride in ethereal solution give the amides, $\text{NO}_2\text{C}_6\text{H}_4\text{SNHC}_{10}\text{H}_7$, while reaction in acetic acid solution results in the formation of nitrophenylnaphthylamine sulfides,

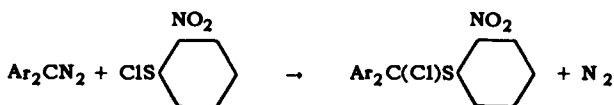


Acetophenone is capable of reacting with sulfenyl chloride to form acetophenone ω -sulfides. The sulfide obtained with *p*-chloro-*o*-nitrophenylsulfenic chloride has been converted by reduction with stannous chloride to a benzothiazine derivative:

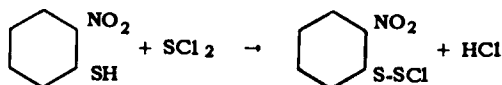


Aromatic sulfenyl chlorides are capable of reacting with ethylene to form aromatic ω -chloroethyl sulfides, $\text{ArS.CH}_2\text{CH}_2\text{Cl}$. Such chloroethyl sulfides have been obtained from phenyl- and *p*-tolylsulfenic chlorides.⁵⁰⁶

Sulfenyl chlorides react smoothly with diazomethane and diaryldiazomethanes to form hemimercapto halides:⁵⁰⁷



A disulfochloride has been obtained through the reaction of *o*-nitrophenylmercaptan with sulfur dichlorides:⁵⁰⁸



SULFONES

Methods of Formation

Sulfones by Use of Sulfonating Agents

Aromatic sulfones, RSO_2R , may be obtained directly from oleum and certain aromatic compounds through the condensation of the sulfonic acid first formed with a molecule of the aromatic body. The use of an excess of the aromatic compound and higher temperatures favor the formation of the sulfone.⁵⁰⁹ Sulfone formation is also favored when the water formed in the reaction is eliminated by distillation or otherwise. It is usually possible to obtain the sulfone as the principal product of the reaction by adjusting the conditions, providing the

aromatic body does not contain a *meta* directing group, or is not heavily substituted. Unsymmetrical aromatic sulfones have been made by passing the vapors of an aromatic hydrocarbon through an aromatic sulfinic acid heated at 125-200°. ⁵¹⁰

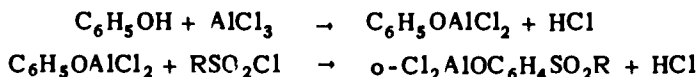
Sulfones have been prepared by the reaction of aromatic bodies with chlorosulfonic acid. Acenaphthene-3,3'-sulfone has been made by heating two moles of the hydrocarbon with one of chlorosulfonic acid at 125-130°. ⁵¹¹

Sulfones by Friedel-Crafts Reaction

Sulfones are formed by the reaction of a sulfonyl halide, ArSO_2Cl , with aromatic compounds in the presence of aluminum chloride or ferric chloride. The reaction involves the formation of an addition compound, and results in the formation of an aluminum halide complex of the sulfone. ⁵¹² For this reason it is essential to use at least one molecular equivalent of the catalyst per mole of the aromatic body. ⁵¹²

The *procedure* may be illustrated by the preparation of *o*-tolyl phenyl sulfone: *o*-Toluenesulfonyl chloride is dissolved in twice its weight of benzene, and an amount of aluminum chloride equal in weight to that of the sulfonyl chloride is added. The mixture is refluxed for half an hour, after which it is poured onto ice, and the excess benzene is distilled off with steam. The sulfone is obtained in 95% yield. ⁵¹³

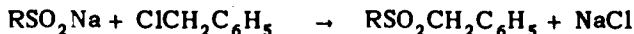
Hydroxyphenyl aryl sulfones may be obtained by heating aluminum chloride with phenol below 100°, then heating the product with a sulfonyl chloride at 130°. ⁵¹⁴ A compound between phenol and aluminum chloride is formed, which reacts with the sulfonic chloride to give the sulfone-aluminum chloride complex:



In the reaction of carbethoxy-*p*-cresol-*m*-sulfonyl chloride with *p*-cresol methyl ether in the presence of aluminum chloride, the carbethoxy group is lost. ⁵¹⁵

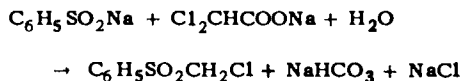
Sulfones by Replacement of Halogens and Other Groups by Sulfonic Groups

Sulfones result through the reaction of alkaline sulfinates with compounds having a reactive halogen. For example, the reaction of a sodium sulfinate with benzyl chloride results in the formation of a benzyl sulfone. ⁴⁹⁵

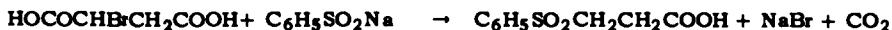


Alkyl arylsulfonylacetates have been made by this method from sodium sulfinates and α -halo esters. ⁵¹⁶ Ethyl phenylsulfonylacetate, $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{COOC}_2\text{H}_5$, has been obtained in 80% yield.

Sodium dichloroacetate gives with sodium benzenesulfinate a chloromethylsulfone. ⁵¹⁷

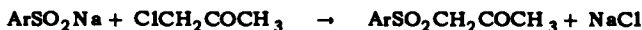


α,α -Dichloropropionic acid gives with sodium benzenesulfinate ethyl α,β -bisphenyl sulfone, $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{C}_6\text{H}_5$. With chloroacetonitrile, the normal arylsulfonylacetoneitrile, $\text{ArSO}_2\text{CH}_2\text{CN}$, is obtained.⁵¹⁸ β -Phenylsulfonylcrotonic acids have been prepared by the reaction of β -chlorocrotonic and β -chloroisocrotonic acids with sodium benzenesulfinate at $160\text{--}180^\circ$.⁵¹⁹ In the reaction of bromosuccinic acid with sodium benzenesulfinate, the carboxyl group adjacent to the sulfonyl group is lost, and β -sulfonylpropionic acid is formed:⁵²⁰

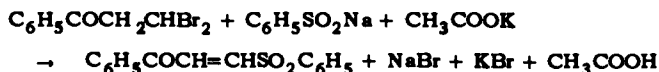


α, β -Dibromosuccinic acid gives ethyl α, β -bisphenyl sulfone.

Aryl sulfonyl acetones have been made by the action of sodium arylsulfonates on chloroacetone in alcoholic solution:⁵²¹



The reaction of β, β -dibromopropiophenone with sodium benzenesulfinate in alcoholic solution in the presence of an alkali metal acetate results in the formation of α -phenylsulfonyl- β -benzoyl ethylene:



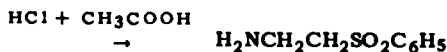
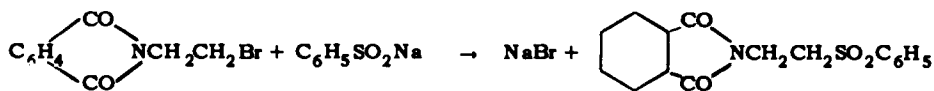
Phenolic methyl sulfones have been prepared by methylating phenolsulfinic acids and heating the resulting methoxyaryl methyl sulfones with hydriodic acid.⁵¹⁵ This appears to be the only satisfactory method of preparation of such sulfones:



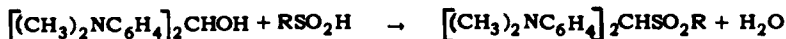
Allyl halides react rapidly with alkali metal sulfonates to yield unsaturated sulfones.⁵²²

The chlorine in *o*-chlorobenzoic acid may be replaced by heating with potassium benzenesulfinate in the presence of a little copper oxide in an autoclave at $125^\circ\text{--}135^\circ$ for two or three hours.

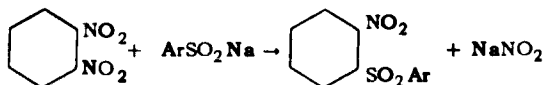
Aminosulfones have been synthesized by the reaction of haloalkyl phthalimides with alkali metal sulfonates, and hydrolysis of the resulting sulfonimine:⁵²³



The hydroxyl group in bis(dimethylaminophenyl)carbinol is replaced with a sulfonic group by reaction with a sulfinic acid:⁵²⁴



The nitro group in *o*-dinitrobenzene is replaceable with a sulfonic group by reaction with a sodium arylsulfinate⁵²⁵



Sulfones by Reaction of Sulfinic Acids with Unsaturated Compounds

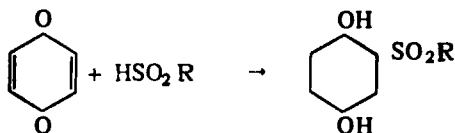
Sulfinic acids add to certain *unsaturated* compounds to form saturated sulfones. Benzenesulfinic acid reacts additively with phenyl vinyl ketone to form phenyl β -phenylsulfonyl ethyl sulfone:



Cinnamic aldehyde gives with toluenesulfinic acid first a sulfonic aldehyde, and finally a disulfone,

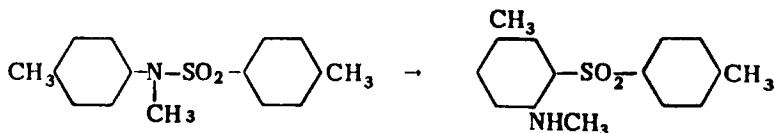


Sulfinic acids add to quinone, forming dihydroxyarylsulfones:⁵²⁶



Sulfones by Rearrangement of Aromatic Sulfamic Acids

Certain aromatic sulfamic acids undergo molecular rearrangement to sulfones:⁵²⁷



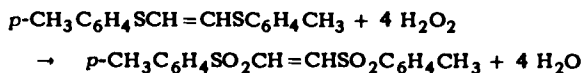
The reaction appears to be general with toluenesulfonyl derivatives of secondary aromatic amines. It is applicable to primary amines, providing no acidic group is present in the para position to the amino group.

Sulfones by Oxidation of Sulfides and by Other Methods

Sulfones result through the oxidation of sulfides. The oxidizing agents generally employed are fuming nitric acid, potassium permanganate, hypochlorous acid, sodium hypochlorite, chromic acid, and hydrogen peroxide. Hydrogen peroxide in solution in acetic acid is a very satisfactory reagent, since it rarely attacks oxidizable groups other than the sulfide and sulfoxide, and gives high yields of the sulfone. Moreover, the isolation of the product in the pure form is greatly simplified when the oxidation is carried out by use of this reagent.

When nitric oxide is used as the oxidizing agent, the reaction often stops at the sulfoxide stage.

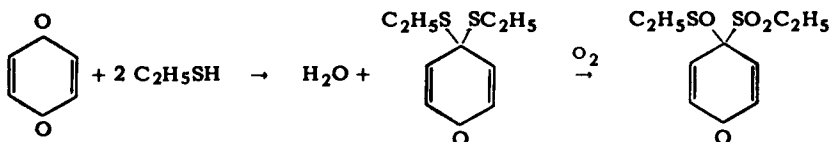
Sulfones of the general type $\text{RSO}_2\text{CH}=\text{CH}_2$ have been obtained by this method from the corresponding sulfides.⁵²⁸ Unsaturated disulfones may be readily obtained from unsaturated disulfides, in which at least one of the unsaturated carbon atoms is attached to a sulfur atom, by oxidation with hydrogen peroxide or potassium permanganate.⁵²⁹



Tetrasulfones, $(\text{RSO}_2\text{CH}_2)_4\text{C}$, have been obtained by oxidation of the corresponding sulfides with an excess of hydrogen peroxide in solution in acetic acid.⁵³⁰ A series of hexa(alkyl sulfonyl)benzenes have been made similarly from the corresponding hexa-sulfides.⁵³¹

2-Hydroxynaphthyl methyl sulfone has been prepared from the corresponding sulfide by oxidation.⁵³²

Quinone disulfones have been made by oxidizing quinone disulfides, which are obtained by the reaction of mercaptans with quinone:⁵³³



Disulfones may be obtained by the careful oxidation of a sulfinic acid:



For example, diphenyldisulfone, $\text{C}_6\text{H}_5\text{SO}_2\text{SO}_2\text{C}_6\text{H}_5$, is formed when five parts of benzenesulfinic acid is dissolved in cold glacial acetic acid, one part of finely powdered potassium permanganate is added and the mixture is allowed to stand for some hours.

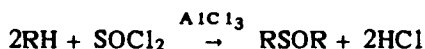
The disulfone separates out on pouring the reaction mixture in water, and nearly neutralizing the liquid with ammonia.⁵³⁴

γ -Disulfones are cleaved to an alcohol by the action of caustic (Stuffer's rule), differing in this respect from other disulfones.⁵³⁵ The reaction proceeds very slowly however.

Sulfones have been obtained in 40 to 80% yield by the reaction of aromatic Grignard reagents with *p*-toluenesulfonates.⁵³⁶ *p*-Bromophenyl methyl sulfone fails to react with magnesium; it would appear, in effect, that aromatic halo-magnesium compounds containing a sulfone group have never been prepared.⁵³⁷

Sulfoxides and Thionylimines

Sulfoxides, RSOR , may be obtained through the reaction of thionyl chloride and an aromatic body in the presence of aluminum chloride:

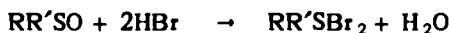


For example diphenyl sulfoxide is prepared by mixing one part by weight of thionyl chloride with three parts of benzene, and adding two parts of aluminum chloride with good cooling and stirring. More benzene is added, as required, to keep the mixture in a fluid condition, and more aluminum chloride is introduced into the mixture in small amounts, until further addition fails to cause the evolution of hydrogen chloride. The mixture is finally heated on the water bath for half an hour and is then poured onto ice. The excess benzene is removed by distillation from the thick, yellow oil which separates, and the residue, which consists of the crude sulfoxide, is cooled to crystallization. The compound is purified by crystallization from ligroin.⁵³⁸

Sulfoxides may be prepared also by the partial oxidation of sulfides.⁵³⁹

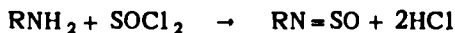
Diphenyl sulfoxide is obtained by gently boiling diphenyl sulfide with five times its weight of nitric acid of 1.1 density for fifteen hours. The sulfoxide separates in good yield on pouring the reaction mixture in ice water.

Sulfoxides possess basic properties and yield chlorides and nitrates of the type $RR'S(OH)Cl$ and $RR'S(OH)NO_3$. With hydrogen bromide they yield dibromides:⁵³⁹

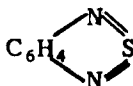


Diiodides are obtained similarly with hydriodic acid.

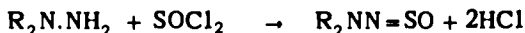
Thionylimines, $RN=SO$, are formed by the reaction of thionyl chloride with primary amines:



Both free aromatic amines and their salts undergo the reaction, which proceeds readily when the amine and the calculated amount of thionyl chloride are added to benzene and the mixture is heated on the water bath.⁵⁴⁰ Tolidine, benzidine, aminostilbene, aminoazobenzene, and diaminoazobenzene all react well, the diamino compounds giving dithionylimines. *Meta*- and *para*-phenylenediamines give the dithionyl compounds, while *ortho*-phenylenediamine gives *piaz* thiol,⁵⁵²



Halo and nitroarylamines also undergo the reaction, as do the ethers and esters of aminophenols and esters of amino carboxylic acids, but the free aminophenols and aminocarboxylic acids fail to react. Primary and secondary unsymmetrical hydrazines also give thionylimines:



Thionylimines, brought into contact with moisture, react rapidly to form thionamic acids, $RNHSOOH$. Thionamic acids are formed also through the reaction of primary amines with sulfur dioxide:²⁸



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